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Table of Contents

Symposium on Snake Bite.

VENOM YIELDS IN AUSTRALIAN POISONOUS SNAKES.[1]

By N. HAMILTON FAIRLEY, O.B.E., M.D., D.Sc., F.R.C.P.,
AND
BERYL SPLATT, B.Sc.
(*Walter and Eliza Hall Institute of Research, Melbourne Hospital.*)

INTRODUCTION.

AN accurate estimation of the venom yield of any given species of poisonous snake is a matter of fundamental importance not only in assessing its potential lethality to man, but also when the question of specific serum therapy comes under review.

Acton and Knowles[(1)] have pointed out that before an antivenene can be regarded as satisfactory, it must be of such a strength that a quantity capable of being injected intravenously will neutralize *in vivo* the full dose of venom given by a full sized snake in natural surroundings half an hour after its inoculation into the system. Thus, the dosage of venom liable to be injected by any given species must form the basis of any attempt to produce an efficient antidote.

The same observers have also emphasized the fall in the venom yields of poisonous snakes when kept in captivity and have advocated taking only the primary yields[2] obtained within twenty-four hours of capture as affording the best index to the full dose of venom given in nature at a single bite. Owing to the habits of Australian snakes of striking at any near object when first captured or failing this of biting themselves or the bag in which they are carried, the primary venom yields often prove too low. The only method of overcoming this difficulty would be to collect venom in the field immediately after capture of the snake without affording it any opportunity of biting, a procedure which is difficult to accomplish. Our observations show that not infrequently larger quantities of poison may be collected after several weeks' captivity, provided the conditions under which the snakes are kept, are satisfactory. For this reason we prefer to take the maximum yield, irrespective of whether it is primary or secondary, as affording the most reliable index to the quantity of poison likely to be injected by the snake in a wild state.

A series of valuable observations on venom production during natural biting by the Australian colubrides has been recorded by Tidswell[(2)] for black, brown and tiger snakes. The questions of residual venom and of the venom producing capacity of the different species in captivity were not considered.

THE CARE OF SNAKES IN CAPTIVITY.

A factor of great practical importance from the standpoint of antivenene production is the venom producing capacity of different snakes in captivity. This is determined for any given species by dividing the sum total of the primary and the various secondary venom yields by the total number of milkings; figures for the tiger snake, copper-head, death adder and black snake will be found in the different tables embodied in this article.

References constantly occur in the literature to the depreciation in venom yields during captivity and it is obvious that if satisfactory results are to be obtained snakes must be kept under conditions approaching as nearly as possible those existing in Nature. For this purpose their habitat, food supply and distribution need careful study.

The Habitat and Distribution of the Common Venomous Australian Colubrides.

The tiger snake, copper-head and black snake are found in Victoria, South Australia and New South Wales, while the death adder, though it occurs in the last two States, is mainly confined to northern aspects of Australia. Both the brown and the black snake have a widespread geographical distribution and occur along with the death adder in Queensland. Western Australia appears to be poorly represented as far as our most venomous snakes are concerned.

The tiger snake shows considerable adaptability, being met with in flat, dry and stony country as well as in swamps and river flats. Its food consists chiefly of frogs, ground birds and small rodents and it commonly hibernates in logs and root holes.

The copper-head on the other hand is mainly an underground snake. It frequents swamps, adjacent hills and river flats, inhabiting and hibernating in crab holes and old rabbit burrows and living on crustaceans, frogs and ground birds.

The black snake commonly hibernates in old disused rabbits burrows. It is particularly fond of water and like the tiger snake swims well. It is found in the foot hill country bordering river flats to which it returns to feed, and subsists chiefly on frogs, lizards and the like. According to Krefft[(3)] it is very partial to the young of the water rat, *Hydromys leucogaster*.

The brown snake also frequents hilly country coming into the crops of the river flats in search of field mice and other food. It is a shy, fast moving snake and is difficult to keep satisfactorily in captivity. It hibernates in and under logs and in the crevices of rocks in hilly country. Unlike the other common poisonous snakes it is oviparous.

The death adder prefers dry soil, being met with in sandy desert and prickly pear country. It is nocturnal in habit and is the only Australian poisonous snake commonly encountered at night. Frequently it lies motionless until touched when it strikes with amazing rapidity. This snake does not stand cold well and artificially heated cages are essential if they are to survive the winter months in more southern latitudes. When hibernating it is found under prickly pear plants, dead leaves and the like.

[1] This research was carried out under a grant from the Commonwealth Government Department of Health.

[2] The primary yield represents venom collected at the first milking within a short period of arrival at the Zoological Gardens, whereas the secondary yields refer to all subsequent collections during captivity.

The Feeding of Captive Snakes.

The different species of ophidia utilized in the present investigation were kept in separate large glass cages in the Reptile House at the Zoological Gardens, Melbourne, and were most skilfully handled and cared for by Mr. T. Eades who also did the field collecting in Queensland, New South Wales and Victoria.

During the winter months the cages are artificially heated and many of our snakes survived the cold weather, but the absence of sunlight and fresh air must ultimately be reflected in the health of captive ophidia and lead to depreciation in venom yields. A snake park such as Brazil[(4)] devised at the Butantan Serum Institute, São Paulo, affords an ideal confining environment, while the institution of ultraviolet radiation plant such as is established at the London Zoological Gardens is proving of material benefit for reptiles caged there. For economic reasons such ideal housing conditions are not yet available in this State, but despite this fact the collection of venom has been organized on a scale which has amply justified the Director of the Commonwealth Serum Laboratories in commencing the manufacture of antivenenes for the tiger snake and the death adder.

Snakes being carnivorous, every effort was made to supply each species with its natural food. Water was constantly available in adequate quantities and living frogs, mice and sparrows were placed in the cages at stated intervals, being caught and devoured with avidity as a general rule.

With the Australian colubrines we have found it inadvisable to give food for a week after the collection of venom, while a clear interval of fourteen days' starvation should precede the next milking. Thus if snakes are milked at the beginning of the first, fifth and ninth weeks, they should be fed during the second, sixth and tenth weeks but not earlier. This is a matter of some moment for Delezenne[(5)] showed that snake venoms contain a kinase which activates the pancreatic juice and plays an important rôle in ophidian digestion.

Feeding a reptile whose venom supply has just been depleted, is unphysiological and may be frought with serious consequences. It is equally unsatisfactory to attempt to milk a snake whose parotid secretion (poison gland) has and still is being expended in digesting a repast so formidable in quantity and quality as that represented by feathered birds, bony rodents or crustaceans.

At the Butantan Serum Institute no effort is made to feed captive snakes. Brazil[(4)] found that even without food the Brazilian snakes continued to yield venom for seven or eight months and owing to their excellently organized system of supplying farmers with antivenene in exchange for living snakes adequate supplies of reptiles for replacement purposes were always available.

At the Haffkine Institute, Bombay, on the other hand, the cobras and Russell's vipers are kept in small cages, one for each snake. They are milked and fed artificially at fortnightly intervals with egg beaten up in milk, which is administered through a glass funnel thrust down the œsophagus. Living rats are also supplied.

As adequate venom supplies are collected at these institutes for Brazil and India respectively, it is obvious that each country must determine by observation on its own snakes that method which is most suitable for its own requirements.

Ophidian Diseases.

Observations will later be recorded showing the effect of starvation and disease in lowering the venom yields of snakes.

A most serious malady and one producing emaciation, anæmia and oft-times death was caused by a lung fluke identified by Professor Harvey Johnson, of Adelaide, as *Dolichopera maculpini* (Nicoll). These trematodes inhabit the trachea, tracheal lung and the true lung in which situation they may be found adherent to pulmonary tissue. In Figure XI a photomicrograph is shown in which lung substance is being actually engulfed in the prehensile anterior sucker of a sectioned fluke.

In the more severe infestations these parasites invade the buccal cavity especially during the later stages of the disease, a finding which probably accounts for the apparent increase in disease incidence after capture. The intermediary host or hosts implicated in the life cycle are unknown.

Ectoparasites in the shape of blood sucking ticks were also frequently observed, the head being deeply buried between the imbricated dorsal and lateral body scales. They were readily removed and did not appear to affect the health of their host, though they would do so indirectly were they the vectors of protozoal blood diseases affecting the reptilia.

One malady originating locally in the reptile house and acquired after captivity was attributable to the common bacon beetle, *Dermestes cadaverinus* (Fabr). Its larvæ were not infrequently found invading the tissues of snakes which had deep lesions of the cuticle, the unfortunate reptiles sometimes being devoured while still alive. On this account care had to be taken not to sear the subcaudal scales too deeply for identification purposes. These larvæ proved excellent scavengers and were used for purposes of cleaning the skull in osteological preparations. It is interesting to note that the venom gland itself often had to be dissected away owing to the refusal or reluctance of *Dermestes cadaverinus* to eat it, though all the other soft tissues were devoured readily.

METHODS OF COLLECTING VENOM.

The identification of individual snakes of one species kept together in large cages was not satisfactorily solved until the method of searing a given subcaudal or ventral scale was evolved, the vent being taken on the anatomical landmark from which the scales were counted. By this means each snake was permanently numbered.

When venom was being collected the snakes were removed by a mechanical stick devised by Mr. Eades

subsequently being held by hand during the actual process of biting and milking.

A rubber capped container is essential in order to prevent dilution of the venom with saliva and its contamination with the contents of the buccal cavity. We found that an ounce medicinal glass measure covered with dental sheet rubber kept in position by elastic bands attached about one and a quarter centimetres from the top, proved an excellent receptacle for this purpose. For convenience of transport these glasses were packed in boxes containing twenty-five separate compartments.

The snake on biting pierces the rubber sheeting with its grooved fangs, while the rubber covered sides of the glass measure afford quite satisfactory fixation for the lower jaws during the actual ejection of the poison, a matter of importance where colubrides are concerned. The reserve venom is expelled by digital massage over the poison glands which are situated behind the eyes in the vicinity of the fifth and sixth supralabial and the lowest temporal scales. This process is technically known as milking.

Snake venom is a mixed salivary secretion composed of the products of the serous parotid gland (venom gland) and of the supralabial mucous glands which pour in their secretions along the course of the venom duct. It varies in colour, being often limpid and colourless, but at other times it is straw coloured or even a bright yellow. Occasionally it may be slightly turbid, a finding which is much more common in poison collected at the terminal milking. Its viscosity varies according to its mucoid content and on drying it forms whitish or yellowish crystalline-like brittle plaques in which state it retains its potency unimpaired for many years.

The Weight of Dry and Fluid Venoms.

After collection the fluid venom was immediately taken to the laboratory, the rubber sheeting slit open and each labelled receptacle placed in a desiccator containing calcium chloride or sulphuric acid and dried under negative pressure to a constant weight. For ordinary purposes only the dried weight was determined, but eighteen death adder venoms were weighed in both the fluid and dried state and similar observations were made in a number of bulk milkings from tiger snakes. The results are recorded in Table I.

Martin[6] recorded variations of from 12% to 67% in the total solids of different specimens of black snake venom and pointed out the fundamental fallacy underlying the use of fluid venoms in the various experiments of the committee appointed by the Medical Society of Victoria in 1875 to inquire into snake bite. Tidswell[2] found the average total solids in sixty-seven observations on tiger snake venom to equal 26·4%.

TABLE I.

Observations on the Weight of Fluid and Dried Venoms.

Species of Snake.	Fluid Venom in Grammes.	Dry Venom in Grammes.	Percentage of Total Solids.
Tiger snake	1·452	0·306	20·4
Death adder	4·369	1·265	29·0

The total solids in the case of tiger snake venom in this series averaged 20·4%, that in death adders 29·0%. The maximum figure obtained for the latter species was 41·9% and the minimum 19·5%, variations which illustrate the entire unreliability of fluid venom for inoculation experiments unless accompanied by determinations of the total solids in a measured volume.

The Venom Yields on Biting and Milking.

When a snake strikes, it rarely ejaculates the whole of the contents of its venom glands. Acton and Knowles[7] studied this question in India where they found that about five-eighths of the total venom in the glands of the cobra and five-sevenths of that in the Phoorsa (*Echis carinata*) were yielded by a good bite.

Residual Venom.

During the present investigation seventy-five observations were made on the residual venom yields of the death adder and thirty-five in the case of the tiger snake. These snakes were allowed to bite naturally and were generally left for a minute or so until they showed some spontaneous inclination to relax their powerful grip on the rubber-covered glass measure before substituting another in which to receive the reserve venom. Naturally during this period more than one ejection of poison was sometimes made.

The results of this series of observations may be studied in Tables II and III.

For tiger snakes the average total yield equalled 43·5 milligrammes of which 29·3 milligrammes were ejected during biting and 14·1 milligrammes on milking. Larger yields were recorded for the death adder, the average total being 79·1 milligrammes. Of this 57·6 milligrammes were given on biting and 21·6 milligrammes on milking (see Table II).

TABLE II.

Observations on Reserve Venom obtained by milking Snakes which have first bitten naturally.

Species of Snake.	Number of Observations.	Average Venom Yield in Milligrammes.			Percentage of Reserve Venom.		
		Total.	Biting.	Milking.	Average.	Maximum.	Minimum.
Tiger	35	43·5	29·3	14·1	27·2	81·3	4·8
Death adder	75	79·1	57·6	21·6	25·5	85·1	0·0

The figures in the Average column are obtained by dividing the sum of the percentages of reserve venom found at each milking by the number of milkings

The mean of the percentages of reserve venom in seventy-five different observations on the death adder equalled 25·5%, the maximum individual yield being 85·1% and the minimum 0·0%. In two instances no venom was obtained on milking, the entire contents of the gland having been expelled in the process of biting.

Similar findings were recorded in the thirty-five observations on tiger snakes, the average of the percentages of reserve venom proving to be 27·2. The maximum individual yield was 81·3% and the minimum 4·8% (see Table II).

In Table III the individual quantities of reserve venom expressed as percentages of the total yield are arranged in an ascending series of groupings.

TABLE III.

The Frequency Distribution of Reserve Venom found in Death Adders and Tiger Snakes which have bitten naturally.

Percentage.	Death Adder.	Tiger Snake.
0– 9·9	18	7
10–19·9	12	5
20–29·9	21	10
30–39·9	9	7
40–49·9	9	3
50–59·9	2	2
60–69·9	1	0
70–79·9	2	0
80–89·9	1	1
TOTAL OBSERVATIONS ..	75	35

In two instances no reserve venom was obtained, all having been ejected during biting.

The great variations in the amounts of venom remaining in the poison glands after biting are here very evident. The Australian colubrides undoubtedly exert a considerable degree of control over the amount of venom actually delivered on striking and can also voluntarily withhold the contents of one gland while injecting the other. This has been repeatedly observed during the present study. In the case of death adders and tiger snakes the venom ejected on biting averages about three-quarters of the total, but occasionally as much as four-fifths are held in reserve, while in others all is expelled.

We have already seen that the maximum yield given at a good bite is of fundamental importance in standardizing the strength of antivenene for any given species of snake and for this purpose it is probably a safer procedure to base one's estimate on the total contents of the venom gland rather than on any fraction of this amount, even though in most instances only a portion be injected.

Is a Snake Which Has Recently Struck Still Dangerous?

Another question which is continually arising, has regard to the potential danger of a snake which has recently struck. In Brazil it is common teaching that such snakes are rendered temporarily non-poisonous and may be caught with impunity owing to the depletion of their supply of venom. This may be the case with species of *Lachesis* whose detrusor poison mechanism is powerfully developed, and whose venom is much less potent per milligramme than that of the Australian colubrines, but in this country snakes do often remain venomous after biting as the observations in Table IV indicate.

It is only possible to get separate successive yields where the snake voluntarily releases his hold after a snap bite. Not infrequently tiger snakes and death adders refuse to relax their temporal muscles sufficiently during separate bites to enable the substitution of one rubber-covered glass for another. This was accomplished, however, in the case of the twelve death adders and the six tiger snakes dealt with in Table IV, the results of which show quite definitely that on occasions considerable quantities of these highly lethal venoms may be ejected at the second or even the third bite without completely depleting the reserve venom as revealed by milking. Our view is that all the more poisonous Australian colubrides are dangerous, no matter how often they have bitten, as long as their poison glands contain reserve venom. This can best be removed by efficient milking and when thoroughly carried out it generally takes several days before even small quantities of poison are demonstrable on biting.

TABLE IV.

The Amounts of Venom yielded on Repeated Bites by Death Adders and Tiger Snakes.

Species of Snake.	Venom Yields in Milligrammes.				
	1st Bite.	2nd Bite.	3rd Bite.	Milking.	Total.
Death adder ..	37·2	41·2	12·0	20·2	110·6
	56·1	20·4	—	3·4	79·9
	36·4	23·3	—	17·0	76·7
	60·0	27·2	—	29·0	116·2
	66·2	22·5	—	21·6	110·3
	40·2	13·4	—	38·2	91·8
	38·8	29·6	—	24·5	92·9[1]
	47·4	4·2	17·0	0·8	69·4
	36·2	16·0	2·6	1·2	56·0
	14·6	15·2	—	0·0	29·8
	30·4	18·6	—	21·5	70·5
	101·2	29·8	8·9	18·6	158·5
Tiger snake ..	81·6	44·5	—	18·6	144·7
	33·8	16·4	3·6	54·2	108·0
	33·7	5·2	—	2·0	40·9
	46·4	7·3	—	14·3	68·0
	13·2	2·5	4·0[1]	5·9	28·6
	23·0	7·5	—	3·5	34·0

[1] This snake yielded on the fourth bite 0·6 milligramme and the fifth bite 2·4 milligrammes.

THE VENOM YIELDS OF THE TIGER SNAKE.

Tidswell[(2)] found the average yield of dried venom based on a series of sixty-seven observations on tiger snakes (*Notechis scutatus*) to be 26·21 milligrammes. The maximum equalled 41·65 milligrammes and the minimum 21·3 milligrammes. Martin[(6)] reported the maximum yield for this species as 73 milligrammes. These figures represent poison collected during natural biting and do not include residual venom obtained by milking. This no doubt constitutes one of the reasons why Tidswell's figures are lower than the series recorded below.

The Total Primary and Secondary Yields.

The total venom yield is composed of the poison ejected by natural biting *plus* the reserve venom

obtained by milking and the results of sixty-eight observations in a series of twenty tiger snakes are recorded in Table V.

The primary yields, that is those obtained shortly after capture, averaged 34·9 milligrammes, while the average for the series of secondary yields was 36·9 milligrammes. There was therefore no demonstrable falling off in venom production during the few months in which subsequent observations were made. The average yield throughout the whole period of captivity amounted to 35·9 milligrammes per snake.

the highest to 155·0 milligrammes In two other snakes the total yields amounted to 98·3 and 112·2 milligrammes respectively.

The Relationship of the Venom Yield to Certain External Characteristics, Dentition and Disease.

Apart from the existence of certain diseases, such as pulmonary fluke due to *Dolichopera maculpini* (Nicoll), the poison yields of snakes vary within considerable limits (see Graph I) and when venom is required in quantity for the production of antivenene, it obviously becomes a matter of importance

TABLE V.

The Total Venom Yields from Twenty Healthy Tiger Snakes milked at approximately Monthly Intervals.

Identification of Snake.	Length in Centimetres.	Distance between Fangs (Centimetres).	Weight in Grammes.	Primary Yield.	Secondary Dry Venom Yields.						Average Yield during Captivity.
					2nd.	3rd.	4th.	5th.	6th.	Average.	
"X"	120·0	1·85	426	100·0	74·6	70·0	112·2[1]	—	—	85·1	89·2
"Y"	111·0	1·65	372	22·4	28·6	15·0	35·6[1]	—	—	26·4	25·4
"A"	101·5	—	282	41·3	57·3[1]	—	—	—	—	57·3	49·3
1	119·0	1·75	544	68·0	144·7	108·0	155·0[1]	—	—	135·9	118·9
3	98·0	1·57	444	—	42·7	43·8[1]	—	—	—	43·3	43·25
4	99·0	1·40	459	33·0[1]	27·4	—	—	—	—	27·4	30·20
5	107·0	1·40	—	20·7	33·4	37·7[1]	—	—	—	35·6	30·6
6	98·0	1·57	388	37·2[1]	13·4	28·8	2·4	—	—	14·9	20·45
9	105·0	1·67	277	98·3[1]	67·2	28·0	52·3	—	—	49·2	61·45
10	93·0	1·40	404	4·6	6·4[1]	5·2	—	—	—	5·8	5·4
11	97·0	1·50	264	24·4	38·8[1]	—	—	—	—	38·8	31·4
12	99·0	1·50	314	22·5	7·2	42·9[1]	—	—	—	25·0	24·2
13	93·0	1·40	322	40·9	39·8	48·1[1]	—	—	—	44·0	42·9
14	99·0	1·30	306	38·8[1]	7·3	30·4	30·5	13·0	37·4	23·7	26·2
15	93·5	1·28	236	26·5[1]	22·2	—	—	—	—	22·2	24·35
16	94·0	1·29	217	2·9	23·4	11·2	36·3[1]	12·3	—	20·8	17·22
17	85·5	1·17	199	21·8	16·8	29·2	35·2[1]	—	—	27·1	25·75
18	74·0	1·08	122	7·3	7·4[1]	—	—	—	—	7·4	7·35
19	95·5	1·35	192	18·6[1]	2·3	—	—	—	—	2·3	10·45
20	112·5	1·55	389	34·8[1]	—	—	—	—	—	—	34·8
AVERAGE TOTALS ..	99·7	1·45	324	34·9	34·8	38·3	57·4	12·7	37·4	36·93	35·9

[1] Maximal yield for this snake.
The average of the maximal yields was 47·2 milligrammes.

The Maximal Venom Yield.

For reasons already outlined the maximal yield for each individual snake was taken as most nearly approaching its natural output of poison in a wild state and the average maximal yield on this basis amounted to 47·2 milligrammes of dried venom. The frequency distributions are given in Table VI.

TABLE VI.

The Frequency Distribution of the Maximal Venom Yields observed in Twenty Tiger Snakes.

Maximal Yield of Dry Venom in Milligrammes.	Number of Snakes.
1– 10	2
11– 20	1
21– 30	1
31– 40	9
41– 50	3
51– 60	1
91–100	1
111–120	1
151–160	1
Average 47·2 milligrammes	Total 20

It will be seen that twelve out of the total twenty snakes yielded from thirty-one to fifty milligrammes. Four exceeded fifty milligrammes, while the remaining four fell below thirty milligrammes. Actually the lowest yield amounted to 6·4 milligrammes and

to be able to select individual snakes which are likely to afford a sustained venom yield during captivity. For this purpose certain readily ascertainable characteristics, such as length, weight and distance between the fangs, were compared with the average venom yields in order to determine if any correlation existed between them. The latter figure is obtained for each individual snake by dividing the sum total of the primary and the various secondary yields by the number of milkings.

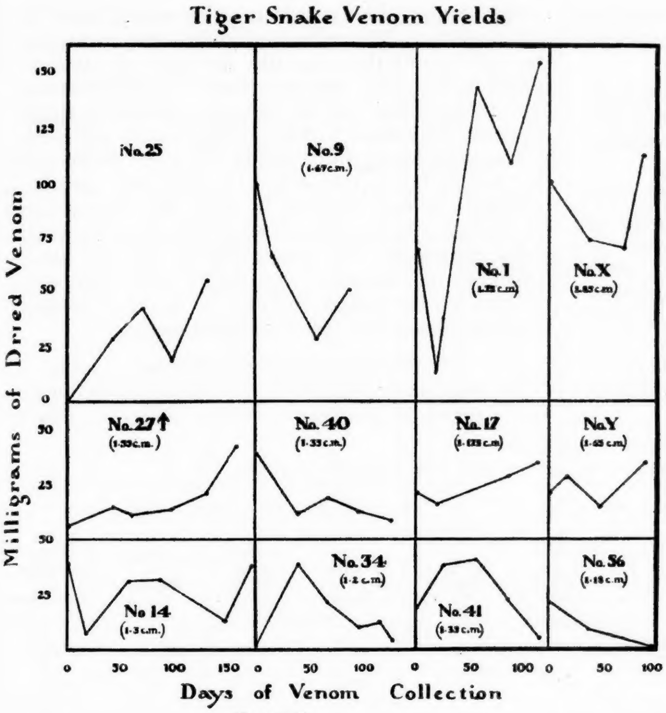
Length of Specimens.

The length of the twenty specimens under review varied from 74 to 120 centimetres, the average being 99·7 centimetres. In Table VII they are

TABLE VII.

The Relationship between Length and the Average Venom Yield in Twenty Tiger Snakes.

Number of Observations.	Length in Centimetres.	Average Venom Yield in Captivity (Milligrammes).
1	70– 79	7·35
1	80– 89	25·75
10	90– 99	24·98
4	100–109	41·85
3	110–119	59·70
1	120–129	89·20
AVERAGE	99·7	35·9



Graph I.

classified in six different groupings, the average total venom yield for each group being recorded for purposes of comparison.

With the exception of the second and third groups in which the yields are approximately equal, it will be seen that there was a steady increase in the production of venom *pari passu* with increase in length. The best average venom yields occurred in snakes exceeding one hundred centimetres. Tidswell[2] reported that with snakes under three feet in length four out of thirteen (22·2%) died, whereas in bites by specimens exceeding this length ten out of twenty-six (38·5%) terminated fatally.

Weight of Specimens.

The figures for the lightest and heaviest snakes were 122 and 544 grammes respectively, while the nineteen comprising the present series averaged 324 grammes. The relationship between the different weight groups and average venom yield is recorded in Table VIII.

Table VIII.

The Relationship between Weight and the Average Venom Yields in Nineteen Tiger Snakes.

Number of Observations.	Weight of Snake in Grammes.	Average Venom Yield in Captivity (Milligrammes).
3	100–199	14·5
5	200–299	36·7
5	300–399	30·7
5	400–499	37·7
1	500–599	118·9

It will be noted that the yields in the second and fourth groups approximate the intermediate third group showing a lower average figure than either. Snakes under two hundred grammes in weight were poorer venom producers, but any specimen exceeding this figure would appear suitable for milking purposes.

The Relationship Existing Between the Distance Separating the Fangs and the Venom Yield.

In another paper dealing with ophidian dentition the technique of taking impressions of the bite in dental wax and subsequently measuring the distance between the fangs is described. It need not, therefore, be further considered. Our immediate problem concerns venom production and in Table IX nineteen tiger snakes have been classified into five groups according to this measurement and their average and maximal venom yields compared.

It will be seen that as the distance between the fangs increases, so does venom production. This correlation holds good for the average yield during captivity as well as the average maximal yield. The latter observation is of considerable clinical importance for in snake bite the distance between fang punctures can be measured. Other things being equal, the further the fangs are apart, the greater the dose of poison injected and the graver the prognosis. In this series the shortest intervening distance was 1·08 centimetres and the greatest 1·85 centimetres, the average being 1·45 centimetres (see Table V).

Table IX.

The Distance separating the Fangs and Venom Yields in Nineteen Tiger Snakes.

Number of Observations.	Distance separating the Fangs in Centimetres.	The Average Venom Yields (Milligrammes) during Captivity.	The Average of the Maximal Yields (Milligrammes) observed.
2	1·0–1·19	16·6	21·3
4	1·2–1·39	19·6	30·1
9	1·4–1·59	29·2	35·9
3	1·6–1·79	68·6	96·3
1	1·8–1·99	89·2	112·2

The Effects of Starvation and Disease.

During the course of these investigations an interesting opportunity occurred for comparing the primary and secondary venom yields of sixty semi-starved fluke infested snakes coming from a drought stricken area near Swan Hill, with twenty healthy tiger snakes obtained from the Mitta Valley where water and animal life was abundant. The results are incorporated in Table X along with certain average external measurements dealt with in preceding sections. It will be seen that venom production proved more than three times greater in the healthy Mitta Valley snakes than in those from Swan Hill. Six of the latter series yielded from 0·0 to 0·1 milli-

gramme of venom, the adverse environmental conditions having so decreased their parotid secretion (venom) as to render them non-poisonous.

The data as presented in Table X are not strictly comparable since the average length as well as the distance between the fangs of the healthy snakes exceeded the semi-starved series.

With the object of making the two series more comparable they have been rearranged in groups in Table XI according to the distance between the fangs and the average maximal venom yield of each group is compared. In all instances the yields of the healthy snakes exceeded those in the semi-starved series and in the last group (1·4 to 1·59 centimetres) it proved almost twice as great. The disparity, however, was not as great as the findings in Table X indicated.

milligrammes, the average for the series being 78·2 milligrammes. The secondary yields obtained during the subsequent three months are also detailed and it will be seen that they averaged 57·1 milligrammes. The mean yield of all venoms collected during captivity amounted to 64·9 milligrammes per snake, this species being much the best venom producer of the Australian colubrides. Despite this fact it is the shortest and lightest of them all, the average length being 63·7 centimetres and the average weight 196·6 grammes. Its large poison glands, strong musculature, mobile long fangs and the great toxicity of its venom combine to make it perhaps the most deadly of all terrestrial snakes.

The Maximal Venom Yields.

The maximal yield for each individual snake was again taken in preference to the primary yield as

TABLE X.

The Average Venom Yields in Tiger Snakes derived from the Mitta Valley and Swan Hill.[1]

Source of Origin of Snake.	Total Number of Snakes Examined.	Measurement of Size.			Dry Venom Yield in Milligrammes.				
		Average Length in Centimetres.	Average Weight in Grammes.	Distance between Fangs (Centimetres).	Average Primary Yield.	Average Secondary Yield.	Average Yield during Captivity.	Average of Maximal Yields.	Total Number of Observations.
Mitta Valley	20	99·7	324·0	1·45	34·9	36·9	35·9	47·2	62
Swan Hill	60	89·6	220·5	1·22	9·5	10·4	10·2	15·2	134

[1] These tiger snakes came from a drought stricken area (Swan Hill); on an average they were smaller in size and were heavily infested with lung fluke (*Dolichopera macalpini*).

Many factors such as captivity, hibernation, ecdysis, ovulation and recent feeding are recognized as leading to reduced venom production and the present findings indicate that the adverse influence of drought and ophidian disease may lead to similar results.

THE VENOM YIELDS OF THE DEATH ADDER.

Only two isolated observations on the venom yield of the death adder (*Ancanthophis antarcticus*) have been previously reported. These were made by Tidswell,[2] the first yield amounting to 42·4 milligrammes of dried venom and the second to 72·5 milligrammes.

The Total Primary and Secondary Yields.

The primary yields from forty-one mature death adders are recorded in Table XII. The maximum equalled 205·0 milligrammes and the minimum 11·2

most nearly approximating to the output of poison in the wild state. The highest individual maximal yield was 235·6 milligrammes and the lowest 23·3 milligrammes, the average being 84·7 milligrammes. The frequency distributions are grouped in Table XIII, in which it is seen that of the forty-one snakes, eighteen yielded from 80·0 to 119·9 milligrammes, fourteen from 40·0 to 79·7 milligrammes and four from 20·0 to 39·9 milligrammes. In five specimens the output varied between 120 and 240 milligrammes.

It is interesting to note that of the maximal individual yields twenty were primary and only sixteen were secondary. In the other four instances only single yields were obtained. With the death adder the primary venom yields are generally satisfactory, as unlike the tiger, black and brown snakes it does not exhaust its venom supply after capture in futile striking at inanimate objects.

TABLE XI.

The Effect of Semi-starvation and Ophidian Disease in Decreasing the Maximal Venom Yields of Notechis scutatus.

Distance between Fangs in Centimetres.	Mitta Valley Snakes.		Swan Hill Snakes.	
	Number of Snakes Examined.	Average Maximal Venom Yield (Milligrammes).	Number of Snakes Examined.	Average Maximal Venom Yield (Milligrammes).
1·0–1·19	2	21·3 (7·4–35·2)	13	15·7 (6·4–28·2)
1·2–1·39	6	24·6 (13·4–38·8)	18	15·4 (2·4–41·6)
1·4–1·59	10	34·6 (6·4–48·1)	9	17·7 (6·1–43·8)

The tiger snakes came from a drought-stricken area (Swan Hill) and were heavily infested with lung fluke.

TABLE XII.

The Venom Yield in Forty-one Mature Death Adders milked at approximately Monthly Intervals.

Identification Number of Snake.	Length in Centimetres.	Weight in Grammes.	Distance between the Fangs in Centimetres.	Venom Yield in Milligrammes.					
				Primary Yield.	Secondary Yields.				Average during Captivity.
					2nd.	3rd.	4th.	Average Secondary Yield.	
2	73·0	370	1·61	110·0[1]	97·0	93·6	—	95·3	100·2
3	70·2	280	2·25	105·8[1]	—	—	—	—	105·8
4	64·0	169	1·55	90·6[1]	69·9	81·8	—	75·85	80·77
5	64·0	169	1·4	110·6[1]	77·2	74·0	89·4	80·2	87·8
6	68·0	265	1·77	115·3[1]	105·4	79·9	98·8	94·7	99·85
7	38·0	150	1·25	38·3	41·0[1]	18·0	31·4	30·13	32·18
8	51·5	105	—	—	—	—	45·6	45·6	45·6
9	65·0	290	1·85	45·7	96·8[1]	87·9	—	92·35	76·8
10	62·5	155	1·65	29·5	28·8	42·9[1]	—	35·85	33·7
11	66·5	240	1·45	36·6	88·4[1]	41·7	55·4	61·83	55·52
12	72·0	210	1·65	54·0[1]	38·0	11·6	—	24·8	34·53
13	45·5	75	1·25	11·2	23·3[1]	0·0	15·8	19·55	16·76
14	66·0	215	1·52	76·7[1]	12·5	32·8	72·8	39·37	48·7
15	57·5	90	1·52	28·2	53·0[1]	—	—	53·0	40·6
16	66·5	160	1·75	90·5[1]	12·2	56·9	—	34·55	53·2
17	65·0	235	1·48	116·2[1]	—	—	41·1	41·1	78·65
18	49·5	105	1·1	32·8	40·5[1]	18·3	24·1	27·63	28·9
19	71·5	230	1·75	110·3[1]	91·8	43·8	71·6	69·06	79·4
20	73·0	270	1·3	78·5[1]	51·4	16·2	—	33·8	48·7
21	67·0	227	1·77	46·1	—	67·2[1]	—	67·2	56·65
22	67·0	212	1·53	92·9[1]	69·4	15·6	47·5	44·1	56·35
23	47·0	77	1·3	20·4	22·0[1]	15·8	—	18·9	19·4
24	64·0	144	1·43	80·9	—	—	—	—	80·9
25	70·0	265	1·73	205·0	96·1	92·5	235·6[1]	141·4	157·3
26	48·0	80	1·15	49·4[1]	23·6	30·0	—	26·8	34·0
27	73·3	285	1·725	101·4[1]	—	56·0	62·4	59·2	73·27
28	73·0	237	1·75	48·5	94·4[1]	37·8	53·1	61·8	58·45
29	63·0	150	1·75	59·6	—	—	—	—	59·6
30	72·5	242	1·72	98·4	106·0[1]	69·1	55·8	76·97	82·33
31	61·5	125	1·53	22·0[1]	11·4	—	—	11·4	16·7
32	69·0	223	1·83	145·5	117·5	40·6	153·5[1]	103·87	114·28
33	70·0	310	1·53	83·6[1]	78·6	69·8	32·0	60·13	66·0
34	72·0	270	1·77	123·0[1]	97·6	120·8	—	109·2	113·8
35	67·0	160	1·58	47·7	68·0[1]	56·0	—	62·0	57·23
36	68·0	228	1·9	95·8[1]	59·1	—	—	59·1	77·45
37	64·0	195	1·6	70·5[1]	20·5	—	—	20·5	45·5
38	69·0	265	1·85	161·0[1]	158·5	41·5	—	100·0	120·3
39	61·5	175	1·6	82·0[1]	63·7	70·6	65·8	66·7	70·53
40	58·0	105	1·15	46·8	49·0[1]	39·6	28·7	39·43	41·25
41	66·0	195	1·8	129·4[1]	69·6	65·1	—	67·35	88·03
42	51·0	100	1·26	36·9	26·2	21·8	8·0	8·7	23·23
AVERAGES.. ..	63·7	196·6	1·58	78·2	63·5	50·3	64·4	57·1	64·9

[1] The maximal yield, the total average for the whole series, was 84·7 milligrammes.

The Relationship of the Venom Yield to Certain External Characteristics, Dentition and Disease.

Length of Specimens.

The length of these forty-one specimens varied from 38·0 to 73·3 centimetres, the average being 63·7 centimetres. In Table XIV they are classified into five different groupings and the average of the total venom yield for each group is recorded for purposes of comparison.

It will be seen that with the exception of the first group which contained only one snake, there was a steady increase in the production of poison *pari passu* with increase in length. The best venom producers all measured more than 60·0 centimetres.

TABLE XIII.

The Frequency Distribution of the Maximal Yields in Forty-one Death Adders.

Maximal Yield of Dry Venom in Milligrammes.	Number of Snakes.
20– 39·9	4
40– 59·9	9
60– 79·9	5
80– 99·9	10
100–119·9	8
120–139·9	2
140–159·9	1
160–179·9	1
220–239·9	1
Average 84·7 milligrammes	Total 41

TABLE XIV.

The Relationship between the Length of the Snake and the Average Venom Yield in Captivity. (Forty-one Death Adders.)

Group.	Number of Snakes Examined.	Length of Snake in Centimetres.	Average Venom Yield in Captivity (Milligrammes).
1	1	30–39	32·2
2	4	40–49	24·8
3	4	50–59	37·7
4	21	60–69	69·4
5	11	70–79	83·6

The average length was 63·7 centimetres; the average venom yield was 64·9 milligrammes.

Weight of Specimens.

The heaviest snake of the series was 370 grammes, the lightest 75 grammes, while the average equalled 196·6 grammes. The relationship between the different weight groups and the average venom yield in the forty-one death adders under review is recorded in Table XV.

With the exception of the sixth group which includes only one specimen, increase in weight is

TABLE XV.

The Relationship between the Weight of the Snakes and the Average Venom Yield in Captivity.
(Forty-one Death Adders.)

Group.	Weight in Grammes.	Number of Snakes Examined.	Average Venom Yield in Captivity (Milligrammes).
1	50– 99	4	27·7
2	100–149	7	41·4
3	150–199	9	61·7
4	200–249	11	67·5
5	250–299	8	99·5
6	300–349	1	66·0
7	350–399	1	100·2

The average weight was 196·6 grammes; the average venom yielded in captivity was 64·9 milligrammes.

accompanied by an increase in venom yields. Snakes weighing less than one hundred grammes are relatively poor venom producers and should not be selected for this purpose.

The Distance Between the Fangs and Venom Yield.

In Table XVI the snakes are grouped in an ascending series according to the distances found separating the fang marks taken in impression compound during natural biting. The maximal and the average venom yields during captivity are compared in the different groups. The actual distances were found to vary from 1·1 to 2·25 centimetres, the average being 1·58 centimetres, which exceeds that observed in any of the other species under review.

TABLE XVI.

The Distance separating the Fangs and the Average and Maximal Venom Yields observed in Forty Death Adders during Captivity.

Group.	Distance separating the Fangs in Centimetres.	Number of Snakes Examined.	Average Dry Venom in Milligrammes. Average Yield in Captivity.	Maximal Yield.
1	1·1–1·19	3	34·7	46·3
2	1·2–1·39	5	28·1	40·3
3	1·4–1·59	11	60·4	80·3
4	1·6–1·79	15	74·6	97·4
5	1·8–1·99	5	95·4	127·3
6	2·2–2·39	1	105·8	105·8

With the exception of the first group comprising only three snakes, the average venom yield in captivity was observed to increase *pari passu* with increase in the distance between the fangs, the broad-headed adders with widely separated fangs being the best venom producers.

Similar findings were recorded in regard to the maximal yield which it will be remembered is taken as the index to the potential lethality of a snake in the wild state. There is a steady augmentation in the venom yield with increase in the distance between the fangs except in the first and sixth groups, the former containing three and the latter one snake respectively. As in the case of the tiger snake the distance between the fang punctures affords data of important prognostic significance and it may also have a special value in indicating the amount of antivenene likely to be required in a given case. Other things being equal, a patient whose fang marks are from 1·5 and 2·0 centimetres apart, will have received much more venom than one in whom they are only one centimetre apart, and will need correspondingly larger quantities of antiserum.

The Effects of Disease.

The adult death adders under consideration were generally healthy, but seven specimens harboured lung fluke (*Dolichopera maculpini*) and one showed larval tape worms in the intercostal muscles belonging to an unknown species of bothriocephalid listed by Professor Harvey Johnson as *sparganum sp.* The influence of the former disease in diminishing the venom yields has already been considered.

The Effects of Immaturity on the Venom Yield.

An interesting comparison between venom production in adult and young death adders is afforded by a perusal of Tables XII and XVII. From the latter it will be seen that this group of young adders which averaged 37·0 centimetres in length and 39·3 grammes in weight, showed a mean distance between the fangs of only 0·8 centimetre. The primary yields averaged 10·2 milligrammes, the secondary 10·7 milligrammes, while the average throughout captivity equalled 9·7 milligrammes.

TABLE XVII.

The Venom Yields in Seven Young Death Adders milked at approximately Monthly Intervals.

Identification Number of Snake.	Length in Centimetres.	Weight in Grammes.	Distance between Fangs (Centimetres).*	Dry Venom Yields in Milligrammes. Primary.	Secondary. 2nd.	Secondary. 3rd.	Secondary. 4th.	Secondary. Average.	Average Yield during Captivity.
43	45·5	63·0	0·7	17·2	38·4[1]	—	—	38·4	27·8
44	42·0	53·0	1·05	—	19·6[1]	2·2	15·8	12·5	12·5
45	42·0	58·0	0·75	19·7[1]	9·0	2·5	3·5	5·0	8·7
46	33·5	25·0	1·02	4·2	—	—	—	—	4·2
47	29·5	24·0	1·03	14·2[1]	—	0·6	—	0·6	7·4
48	34·0	30·0	0·85	4·0	8·6	3·0	—	5·8	5·2
49	32·5	22·0	0·98	2·0	0·8	2·4[1]	—	1·6	1·7
AVERAGE	37·0	39·3	0·8	10·2	15·3	2·1	9·7	10·7	9·7

[1] Maximal yields, the average of which was 15·3 milligrammes.

The mean maximal yield for the series was 15·3 milligrammes, just about one-quarter of the amount of venom produced by adult snakes (see Table XII). Naturally immature adders are less likely to inject lethal doses than adult ones and when the snake is not captured, measurement of the distance between the fang marks again affords the best guide to its maturity and cranial development, as well as to the amount of venom likely to have been injected.

The Relationship of the Venom Yield to Certain External Characteristics and Dentition.

Length of Specimens.

The length of the twenty-five specimens varied from 73·5 to 119·0 centimetres, the average for the series being 100·0 centimetres. In Table XX they are classified into five different groupings and the average of the total venom yield for each group is recorded for purposes of comparison.

TABLE XVIII.

The Venom Yields in Twenty-five Copper-heads milked at approximately Fortnightly or Monthly Intervals.

Identification Number of Snake.	Length in Centimetres.	Weight in Grammes.	Distance between Fangs (Centimetres).	Dry Venom in Milligrammes.									Average Yield during Captivity.
				Primary Yield.	Secondary Yield.								
					2nd.	3rd.	4th.	5th.	6th.	7th.	8th.	Average.	
1	94·0	317	1·0	5·8[1]	3·6	2·4	5·8	—	0·0	—	—	3·0	3·5
2	98·0	482	1·15	17·5[1]	6·8	—	1·2	—	12·2	—	—	6·7	9·4
3	119·0	737	1·35	28·2[1]	19·5	11·8	—	5·6	—	—	—	12·3	16·3
4	116·6	612	1·3	14·0	14·4	—	40·7[1]	—	23·4	—	26·2	26·2	23·7
5	108·0	567	1·1	5·0	—	—	—	—	—	—	—	—	5·0
6	112·0	742	1·38	41·1	45·6[1]	18·5	—	20·0	—	—	—	28·0	30·6
7	116·0	616	1·35	61·0[1]	16·8	19·2	—	—	—	—	—	18·0	32·3
8	114·5	672	1·15	31·6[1]	16·9	10·6	—	7·1	—	—	—	11·5	16·5
9	113·0	719	1·26	34·2[1]	28·8	15·2	—	—	—	—	—	22·0	26·1
10	106·0	514	1·45	84·6[1]	77·0	42·8	—	—	—	—	—	59·9	68·1
11	91·0	422	1·1	—	1·0	4·2	—	—	—	10·2[1]	—	5·1	5·1
12	109·0	562	0·95	10·0	11·8[1]	—	—	—	—	—	—	11·8	10·9
13	112·0	617	1·2	57·7	—	—	—	—	—	—	—	—	57·7
14	108·0	474	0·9	5·7[1]	3·0	—	—	—	—	—	—	3·0	4·3
15	102·5	502	0·9	—	25·8[1]	16·5	—	—	—	—	—	21·1	21·1
16	100·0	496	1·15	49·8[1]	12·0	—	—	—	—	—	—	12·0	30·9
17	101·5	334	0·97	7·8	2·2	13·7[1]	—	—	—	—	—	7·9	7·9
18	87·0	314	1·02	27·0	—	—	—	—	—	—	—	—	27·0
19	86·0	194	1·0	6·8[1]	1·3	—	—	—	—	—	—	1·3	4·1
20	93·0	304	1·03	4·7	3·0	3·2	—	5·4[1]	—	—	—	3·9	4·7
21	80·5	194	0·84	14·8[1]	6·8	—	—	—	—	—	—	6·8	10·8
22	77·5	174	1·0	20·2[1]	8·8	—	—	—	—	—	—	8·8	14·5
24	94·0	404	1·16	23·6	—	—	—	—	—	—	—	—	23·6
25	89·5	289	1·0	19·2[1]	7·7	2·4	—	0·0	—	17·0	—	6·8	9·3
26	73·5	159	0·9	2·1[1]	0·0	—	—	—	—	—	—	0·0	1·0
AVERAGE ..	100·0	456·7	1·1	24·9	14·9	13·4	15·9	7·6	11·9	13·6	26·2	13·1	18·5

[1] Maximal yields, the average of which was 25·9 milligrammes.

THE VENOM YIELDS OF THE COPPER-HEAD.

The Total Primary and Secondary Yields.

The primary yields derived from twenty-five copper-heads (*Denisonia superba*) are recorded in Table XVIII, the average for the whole series being 24·9 milligrammes of the dried venom.

The secondary yields were not as satisfactory as the primary, averaging only 13·1 milligrammes, but owing to the fact that the earlier milkings were performed at fortnightly instead of monthly intervals, the results are not strictly comparable to those recorded for the other species. The mean yield throughout captivity amounted to 18·5 milligrammes per snake.

The Maximal Yields.

The highest individual maximal yield equalled 84·6 milligrammes of the dried venom, while the lowest was only 2·1 milligrammes. The series averaged 25·9 milligrammes which is the lowest yield of the four species of Australian colubrides under consideration.

Out of the twenty-five snakes the yields were under twenty milligrammes in twelve. In seven they varied from 20 to 39·9 milligrammes, in four from 40 to 59·9 milligrammes, while in the remaining two they exceeded the latter figure (see Table XIX).

TABLE XIX.

The Group Distribution of the Maximal Venom Yields in Twenty-five Copper Heads.

Maximal Yield in Milligrammes.	Number of Snakes.
0–19·9	12
20–39·9	7
40–59·9	4
60–79·9	1
80–99·9	1

TABLE XX.

The Relationship between the Length of the Snake and the Average Venom Yield in Captivity.
(Twenty-five Copper Heads.)

Group.	Length of Snake (Centimetres).	Number of Snakes Examined.	Average Venom Yield in Captivity (Milligrammes).
1	70– 79·9	2	7·8
2	80– 89·9	4	12·8
3	90– 99·9	5	9·3
4	100–109·9	7	21·2
5	110–119·9	7	29·0

The average length was 100 centimetres; the average yield was 18·5 milligrammes.

It will be observed that with the exception of the third group there is a steady increase in the average

venom yield as the length of snakes in the different groups increases. With one exception the best venom producers all measured over one hundred centimetres in length.

Weight of Specimens.

The weight of the twenty-five specimens varied from 159 to 742 grammes, the average for the series equalling 456·7 grammes and the relationship of this factor to the average venom yield in captivity is traced in Table XXI.

TABLE XXI.

The Relationship between the Weight of the Snake and the Average Venom Yield in Captivity. (Twenty-five Copper Heads.)

Group.	Weight of Snake (Grammes).	Number of Snakes Examined.	Average Venom Yield in Captivity. (milligrammes).
1	100–199	4	7·6
2	200–299	1	9·3
3	300–399	4	10·8
4	400–499	5	14·6
5	500–599	4	26·3
6	600–699	4	32·6
7	700–799	3	24·3

It will be noted that the venom yield increases with increase in weight in six out of the seven groups, the heaviest being exceptional in this regard.

The Distance Between the Fangs and the Venom Yield.

The distance separating the fangs on natural bite was determined for each of the twenty-five snakes. The minimal and maximal measurements were 0·84 and 1·45 centimetres respectively, while the average equalled only 1·1 centimetres.

When grouped in an ascending series according to this factor as has been done in Table XXII it will be observed that both the maximal and the average venom yields obtained during captivity show a progressive increase for each group of snakes as the distance between the fangs widens.

TABLE XXII.

The Distance between the Fangs and the Average and Maximal Venom Yields in Twenty-five Copper Heads during Captivity.

Group.	Distance separating the Fangs in Centimetres.	Number of Snakes Examined.	Average in Milligrammes.	
			Average Yield in Captivity.	Maximal Yield.
1	0·8–0·99	6	11·2	14·7
2	1·0–1·19	12	12·8	18·5
3	1·2–1·39	6	31·1	44·6
4	1·4–1·59	1	68·1	84·6

As in the case of the other colubrides the distance between the fangs of the copper-head affords reliable information regarding the amount of venom likely to have been injected.

The Primary Yields in Another Series of Copper-Heads.

Another batch of fifty-six copper-heads recently collected by Mr. T. Eades and milked by Dr. C. H. Kellaway showed primary yields which were considerably higher than the ones just recorded. The recent collection comprised a greater proportion of large, heavy, broad-headed specimens and variation in the average size of the two series underlies the disparity in their average venom yields.

In the recent series the average primary yield for these fifty-six snakes was 40·1 milligrammes of dried venom. The maximal individual yield recorded equalled 189·6 milligrammes, while two others yielded 132·8 milligrammes and 119·0 milligrammes.

Twenty-eight specimens (50%) with poorer venom yields averaged 13·25 milligrammes, while the remaining twenty-eight (50%) averaged 66·9 milligrammes. In fourteen specially selected snakes the average yield was 77·1 milligrammes.

Commentary.

The primary yields of the combined series comprising eighty-one snakes average 35·6 milligrammes and as little difference was previously found between average primary and average maximal yield in the copper-head (Table XVIII) this figure may safely be taken as a basis for estimating its potential lethality.

It is also interesting to note the close approximation of the primary yields in the tiger snake, black snake and copper-head, the average being 34·9, 37·0 and 35·6 milligrammes respectively.

THE VENOM YIELDS OF BLACK SNAKES.

Tidswell[(2)] reported the average weight of dry venom collected during thirty-two observations on black snakes (*Pseudechis porphyriacus*) to be 12·95 milligrammes, the minimum and maximum yields being 4·6 and 26·0 milligrammes respectively. These figures were based on natural bites only, extraction of residual venom by milking not having been employed. Martin recorded the maximal yield for this species to be 94·0 milligrammes.

In the first series twenty-two observations on the venom yields of six black snakes, all of which were in excellent condition, are recorded (see Table XXIII). Their average length equalled 132·5 centimetres and the average weight 844·2 grammes. The distance between the fangs varied from 1·05 to 1·6 centimetres, the mean being 1·24 centimetres.

The six primary venom yields averaged 37·0 milligrammes and the sixteen secondary yields 31·4 milligrammes, while the average yield for each snake during captivity equalled 34·9 milligrammes. The maximal yields varied from 16·5 to 74·7 milligrammes, the average being 47·2 milligrammes.

In another series of recent observations on fifteen black snakes collected in October shortly after hibernation, the results of the primary yields approximated more closely to those of Tidswell, the minimum and maximal being 0·5 and 50·1 milligrammes respectively and the average equalling 11·3 milligrammes. These lower figures are certainly dependent on the loss of venom resulting from futile striking after capture, a state of affairs which will be revealed by an increase in the venom collected at the next milking.

TABLE XXIII.

The Venom Yields in Six Black Snakes milked at approximately Monthly Intervals.

Identification Number of Snake.	Length in Centimetres.	Weight in Grammes.	Distance between Fangs in Centimetres.	Venom Yield in Milligrammes.						Average Yield throughout Captivity.
				Primary Yield.	Secondary Yield.					
					2nd.	3rd.	4th.	5th.	Average.	
1	132·5	882	1·11	74·7[1]	27·9	—	—	—	27·9	51·3
2	171·5	1,355	1·60	52·1[1]	33·7	24·6	37·2	—	31·8	36·9
3	129·0	950	1·08	26·0	26·2[1]	23·0	—	—	24·5	25·1
4	100·0	417	1·05	25·0	—	23·0	—	38·8[1]	30·9	28·9
5	147·0	1,054	1·39	30·9	74·8[1]	58·0	38·8	69·5	60·3	54·4
6	115·0	407	1·22	13·2	12·0	8·4	16·5[1]	16·0	13·2	13·2
AVERAGE ..	132·5	844·2	1·24	37·0	34·9	27·4	30·8	41·4	31·4	34·9

[1] Maximal yields, the average of which was 47·2 milligrammes.

THE VENOM YIELDS OF BROWN SNAKES.

Tidswell made thirteen observations on the venom yields of brown snakes (*Diemenia textilis*) and found that the average was only 4·8 milligrammes of dry venom. The maximum yield equalled 5·56 and the minimum 4·0 milligrammes.

In our own series of seven snakes of this species no venom was obtained even on milking. Two were excellent specimens which had been recently captured, while five had been caged for a period of nine months before any effort was made to milk them. Even in the largest specimen the interfang measurement did not exceed 1·1 centimetres.

Diemenia textilis is a shy snake and like the krait does not produce satisfactory venom yields in captivity, at least not under the conditions in which our snakes were kept.

There are many authentic cases in the literature, however, of adults dying after being bitten by this snake and it is evident that even though it be a poorer venom producer than other specimens, it must give considerably larger quantities of poison in the wild state than it does in captivity.

A COMPARISON OF THE VENOM YIELDS IN THE DIFFERENT SPECIES.

When the average length and weight of the different species are compared, it will be seen that the black snake is the largest, the copper-head next, the tiger snake third and the death adder much the smallest (see Table XXIV). Contrary to what one would expect the smallest species gave the largest venom yields during captivity. Further when the relative toxicity of the venoms is taken into account it at once becomes evident that it is the larger species which are the least dangerous. In fact there exists an inverse ratio between lethal power and size as far as these four Australian species are concerned. On the other hand, within any given species it is the larger sized snakes which produce the most poison.

The average distance separating the fangs in the different species is of considerable interest, for here the same relationship is demonstrated as has been already shown to exist between the individual members of the same species, that is venom yields increase as interfang measurements become greater. Thus, the death adder, tiger snake, black snake and copper-head series showed mean measurements of 1·58, 1·45, 1·24 and 1·10 centimetres respectively, while their venom yields in captivity averaged 64·9, 35·9, 35·0 and 18·5 milligrammes respectively (see Table XXIV).

It should be noted, however, that the latter figures for copper-head do not include the more recent series of larger sized snakes included in the text. Undoubtedly both their yields and interfang measurements would have been correspondingly greater.

The distance between the fangs really gives an index to the size of the skull which in turn is related to the dimensions of the poison glands and the venom yield. Only when the species has been identified, can interfang measurements be used in estimating size and maturity. It is the broad headed snake which is the best venom producer and the most dangerous.

TABLE XXIV.

The Venom Yields in Different Species of Australian Poisonous Snakes.

Species of Snake.	Number of Snakes Examined.	The Number of Milkings.	Average Length in Centimetres.	Average Weight in Grammes.	Average Distance between Fangs (centimetres).	Dried Venom in Milligrammes.				
						Average Primary Yield.	Average Secondary Yield.	Average Yield during Captivity.	Average Maximal Yield.	Highest Individual Yield for the Species.
Black snake	6	22	132·5	844·2	1·24	37·0	31·4	35·0	47·2	74·8
Copper-head	25	70	100·1	456·7	1·10	24·9	13·1	18·5	25·9	84·6
Tiger snake	20	62	99·7	324·0	1·45	34·9	36·9	35·9	47·2	155·0
Death adder	41	125	63·7	196·6	1·58	78·2	57·1	64·9	84·7	235·6

A more recent series of observations on fifty-six copper-heads of larger average size than the above showed a primary venom yield averaging 40·1 milligrammes. The maximal individual yield equalled 189·6 milligrammes.

Summary and Conclusions.

1. The average percentage of reserve venom demonstrated in the poison glands after biting was 25·5 in the death adder and 27·2 in the tiger snake. Variations of from 0·0% to 85·1% were noted.

2. An Australian colubrine which has recently struck must still be regarded as dangerous and if a snake has to be handled, the entire contents of the venom gland should be immediately removed by milking and not by merely allowing it to bite.

3. The average primary yield, the mean yield during captivity and the average maximal yield were determined in the death adder, the tiger, the copper-head and the black snake.

4. The death adder is the best and the brown snake the poorest venom producer, while the black, copper-head and tiger snakes occupy intermediate positions.

5. Owing to the habits of the Australian snakes the maximal yields afford a better index to the amount of poison liable to be injected in a wild state than the primary yields.

6. The effects of disease, drought and immaturity on the venom yield were specially studied. The commonest ophidian disease was caused by a lung fluke (*Dolichopera maculpini*).

7. Many other factors such as recent feeding, hibernation and shedding of the skin may lead to a decrease in the secretion of the poison glands and the same snake will from time to time manifest considerable variation in its venom yields.

8. Snakes of the same species give greater yields as their weight and length increase.

9. In the various species investigated as well as in different members of any one species the venom yield was found to increase with the distance separating the fangs.

10. The clinical importance of measuring the distance between skin punctures is emphasized. An interfang measurement of less than one centimetre is liable to be associated with a small dose and one of 1·5 to 2·0 centimetres with a large dose of venom.

Acknowledgements.

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Professor Harvey Johnson and Dr. F. M. Burnet have kindly identified different ophidian helminths and ectoparasites met with in the course of the investigation.

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THE VENOM OF NOTECHIS SCUTATUS.[1]

By C. H. Kellaway, M.C., M.D., M.S., M.R.C.P.
(*From the Walter and Eliza Hall Institute, Melbourne.*)

The toxic effects of many snake venoms are well known to vary somewhat in different species of animals. Observations with a venom in a number of different species have, therefore, a definite value in indicating more surely than do observations on a single species the limits within which the certainly lethal dose for man is likely to fall. They are also of use in that variations in the symptomatology and pathological changes following the injection of venom may afford clues for the analysis of its action. The earlier observations of Martin[(1) (2)] largely on the venom of *Pseudechis porphyriacus* and of Tidswell[(3)] on the venom of *Notechis scutatus* were made mainly on dogs and rabbits and for most of the species investigated here no figures for the lethal dose are available in the literature. In the present paper a few observations on horses, cats and monkeys (*Macacus rhesus*) and more numerous ones on rabbits, guinea-pigs, rats and mice are recorded. For the smaller animals the "characteristic" of the venom (Trevan[(4)]) has been determined to eliminate individual variations in susceptibility. This has been done by subcutaneous injection, the use of the intravenous route being excluded by the presence in the venom of an active principle which causes coagulation of the blood (Martin[(1)]). Intravenous injection of doses too small to produce this *in vivo* coagulation may in some species, like similar or larger doses given subcutaneously, cause death with neurotoxic symptoms.

In determining the certainly lethal dose of a venom for any species the average weight of the animals used is of importance, a given dose per kilogram being more toxic for large than for small individuals. The weight of the contents of the alimentary tract also introduces a variable. As far as possible I have used animals whose body weights were within a reasonable range of variation, the weighings being done in the morning before the animals were fed.

Effects in the Horse.

Observations on three horses were made in collaboration with Dr. N. H. Fairley, at the Veterinary Institute. Professor MacCallum and Mr. Albiston kindly assisted at the autopsies. The

[1] This research was carried out under a grant from the Commonwealth Government Department of Health.

venom was administered subcutaneously in a concentration of 0·2 milligramme per cubic centimetre. The results are set out in Table I.

TABLE I.
Effect of Subcutaneous Administration of Venom in Horses.

Weight in Kilograms.	Sex.	Approximate Age.	Dose in Milligramme per Kilograms.	Result.
450	F.	10	0·022	Paralysed after 6 hours 20 minutes and died in 12 hours 55 minutes.
273	M.	25	0·011	Paralysed after 16 hours 10 minutes and died in 28 hours 56 minutes.
315	M. (Gelding)	Uncertain	0·005	Paralysed after 19 hours 19 minutes and died in 50 hours 29 minutes.

These observations are too few for the determination of the lethal dose, but indicate that it is probably not very far removed from 0·005 milligramme per kilogram.

The symptoms exhibited by these three animals were all closely similar. After some hours definite respiratory distress was evident, the *alæ nasi* and the abdominal muscles working, though there was little thoracic movement. The pupils were somewhat dilated. Vaginal hæmorrhage was seen in the mare. No hæmoglobinuria was observed in any of these animals. Paresis occurred first in the hind limbs, then in the fore limbs, thoracic muscles and neck muscles. The abdominal muscles appeared to be affected only very late. Muscular twitching preceded the onset of paresis. Sweating was a very characteristic feature in all these animals.

Post Mortem Findings.

In the first two animals there was extensive bruising round the shoulder where the injection was made, but as they "went down" on that side, this may be perhaps discounted to some extent.

In the first animal there were multiple hæmorrhages in the lungs, associated with hypostatic congestion. Petechial hæmorrhages were seen on the outer surface of the pericardium, in the subperitoneal coat of the small intestine and in the uterus. In the second there were more extensive hæmorrhages in the lungs and hæmorrhages in the adrenals, omentum and kidneys. In the third there were scattered hæmorrhages through the substance of the heart muscle, along the fat round the coronary vessels and streaky spoiling and hæmorrhages in the pulmonary arteries. In the lungs there were extensive areas of hæmorrhage. There were also small hæmorrhages in the adrenals, kidney and pancreas. In all three animals the blood was tarry and in horse number 1 in which the autopsy was carried out shortly after death, the clotting time was twenty minutes. The spleen was enlarged and almost black on section and the liver was intensely congested.

The deaths in these animals were evidently due to neurotoxin, though hæmorrhages were a prominent feature at all autopsies.

EFFECTS IN THE MONKEY.

A few observations were also made in *Macacus rhesus*. The results of subcutaneous injection into the tissues of the hind limb of this venom in a concentration of 0·5 milligramme per cubic centimetre are shown in Table II.

TABLE II.
Effect of Subcutaneous Administration in Monkeys.

Weight in Kilograms.	Dose in Milligramme per Kilogram.	Result.
3·51	0·10	Death in 6¼ hours.
2·635	0·05	Death in 21 hours 25 minutes.
3·25	0·02	Death in 70 hours.

The observations are insufficient in number to do more than to indicate the degree of toxicity of the venom for this species, but the lethal dose is probably not far removed from 0·02 milligramme per kilogram.

The Symptoms.

The animals were unduly quiet and had no appetite and early showed bilateral ptosis and cyanosis. At a later stage they sat huddled up, nodding like a drunken man. In the first monkey bilateral ptosis and cyanosis were evident after two hours, paralysis of the hind and forelimbs appeared after four hours and after five hours the animal appeared to be almost completely paralysed. There was severe dyspnœa even in the earlier stages and before death the respiratory efforts were obviously ineffectual.

In the second monkey there was ptosis in seven hours; paresis of the limb muscles with ataxia in the movements was evident after twelve hours and after eighteen hours the animal was almost completely paralysed. The pupils were moderately dilated before death. In the third animal ptosis and nodding of the head were seen after twenty-one hours, shivering and muscular weakness, particularly in the hind limbs, was present on the second day and death did not occur till late on the third day.

Post Mortem Findings.

In all these animals death apparently resulted from paralysis of respiration, the heart being found still beating after death. Stimulation of the phrenic nerves immediately after death gave good contraction of the diaphragm. The blood was fluid and the clotting times were eight and a half minutes in the first, six minutes in the third, while the blood of the second animal failed to clot in one hour and forty minutes.

In all the animals small areas of hæmorrhages were present in the lung and in the second hæmoptysis had occurred. The right bronchial tract was full of blood and the mouth, œsophagus and stomach contained blood evidently from this source. The upper part of the small intestine was somewhat congested in all three monkeys and contained much

bile-stained mucus. There was congestion of the liver and spleen and of the superficial surface of the *cortex cerebri*. Only one monkey, the third, had hæmoglobinuria.

Effects in the Cat.

The cat appears to be more resistant to the venom than the other species so far studied. The venom was administered subcutaneously in a concentration of 0·5 milligramme per cubic centimetre in the tissues of the flank. Table III shows the results.

TABLE III.
Effects of Administration in the Cat.

Weight in Kilograms.	Sex.	Dose in Milligrammes per Kilogram.	Result.
4·5	M.	1·1	Death in less than 10 hours.
2·9	F.	0·1	Death in 41 hours.
1·7	F.	0·08	Death in 66½ hours.
2·78	F.	0·07	Moderately severe symptoms, recovered by the third day.
2·26	F.	0·07	Moderately severe symptoms, recovered by the third day.
2·6	F.	0·05	Very severe symptoms, paralysed in 22 hours, remained so till fifth day; recovered.
1·58	F.	0·05	Very severe symptoms, paralysed within 22 hours, gradually recovered by the fifth day.
3·47	M.	0·02	Vomited once, 3 hours after the injection; no other symptoms; survived.

The certainly lethal dose is probably about 0·1 milligramme per kilogram.

The animal sometimes vomits within a short time after receiving the injection. In the case of cat 1 this occurred after nine minutes and there were several further attacks of vomiting within the first hour. Respiratory distress may early become evident. Weakness and later paralysis of the limb muscles then appear. The animal lies prone or on its side, the pupils are moderately dilated and death ensues, generally from respiratory failure, though there is circulatory collapse in the later stages.

Cats which received doses which were only just sublethal, showed anorexia and general weakness with paresis of the hind limbs and maximally dilated pupils twenty-two hours after the injection. They were then disinclined to move and the least movement induced dyspnœa. On the second day these symptoms were still more evident. By the third day rapid or gradual improvement had commenced and the pupils were no longer dilated. The last symptom to be lost was in all cases anorexia. During the period in which paresis and general weakness were present, muscular tremor on exertion was a very characteristic feature.

Post Mortem Findings.

There is sometimes a small amount of hæmorrhage and congestion at the site of injection. Congestion and patchy hæmorrhages in the lungs are invariable. The small intestine is also congested and in one animal there were several hæmorrhages within the lumen and in another petechial hæmorrhages were present in the pericardial fat. In no case was hæmoglobinuria observed.

Effects in the Rabbit.

In much of the early work rabbits were used as test animals. Tidswell's observations[3] in agreement with those of C. J. Martin placed the certainly lethal dose by subcutaneous injection at 0·05 milligramme per kilogram and by the intravenous route at about one-tenth this amount.

The Effect of Intravenous Injections.

Tidswell's experiments suggest that the certainly lethal dose of the sample of venom which he used, was 0·004 milligramme per kilogram, though he used 0·005 milligramme as the lethal dose in his protection experiments. My own observations on laboratory strains of long eared rabbits of various colours point to 0·002 milligramme per kilogram as the certainly lethal dose for the venom, when injected in a concentration of 0·01 milligramme per cubic centimetre by the ear vein. Table IV epitomizes the results in rabbits whose average weight was 1·87 kilograms. The extreme weights were 1·42 and 2·43 kilograms, but the weight of more than two-thirds of the animals used lay between 1·7 and 2·0 kilograms. The sexes were evenly distributed. I attempted in all the intravenous injections to use a steady and slow rate of injection. Martin's work[1] with black snake venom has demonstrated the importance of this factor.

TABLE IV.
The Effects of Intravenous Administration in Rabbits.

Number of Animals.	Dose in Milligramme per Kilogram.	Results.
1	0·5	Death in 2 minutes.
2	0·005	Death in 1 minute and in 2 minutes.
2	0·004	Both died in 2 minutes.
9	0·002	Two died in 2½ minutes, one in 2¾ minutes, two in 3 minutes, one in 3½ minutes, two in 4 minutes, and one in 4½ minutes.
3	0·001	One survived, one died in 4¾ minutes, and one in 7 minutes.
2	0·0005	Both survived without symptoms.

The symptoms which follow intravenous injection of tiger snake venom in a lethal dose are very dramatic. During the first minute there may be three or four deep forced respirations and the animal seems a little uneasy. In from one to two minutes the head falls over on one side, the animal makes a short jerky run for ten to fifteen seconds, then falls over on its side and gives a few convulsive kicks. The eyes protrude and after a few feeble and ineffectual respiratory efforts the animal succumbs.

Post Mortem Findings.

In the right auricle and ventricle fibrin appears to have been whipped out as stringy clot and there

is almost invariably some clotting, patchy or solid, in the portal veins and its tributaries. Thrombosis is also frequent in the lung vessels. With larger doses and more rapid death clotting may be universal.

Rabbits which survive immediate death, do not appear to present any symptoms at all. In the few experiments I have made, I have not met with the delayed type of thrombotic death seen in other species nor with death even later following neurotoxic manifestations without thrombosis.

The Effect of Subcutaneous Injection in the Rabbit.

In all cases the injection has been given in the subcutaneous tissues of the flank in a concentration of 0·1 milligramme per cubic centimetre. The average weight of the animals used was 1·7 kilograms and the extremes 2·5 and 1·24, though the weights of nearly all the animals lay between 1·6 and 1·8 kilograms. The sexes were evenly distributed.

The results are set out in Table V.

Table V.
The Effect of Subcutaneous Administration in Rabbits.

Number of Animals.	Dose in Milligramme per Kilogram.	Result.
2	0·06	Death in less than 16½ hours and in 19¼ hours.
4	0·05	Two died in 17½ hours, one in 19¾ hours, and one in 21 hours.
6	0·045	One died in 23 hours, two in 24 hours, one in 28 hours, and two in 30 hours.
10	0·04	Five had severe symptoms but survived, two died in less than 16½ hours, one in 19 hours, one in less than 20 hours, and one in 23 hours.
1	0·035	Death in less than 16½ hours.
11	0·03	Three had severe symptoms but survived, one died in 30 hours, two in less than 44 hours, one in 44 hours, two in less than 72 hours, one in 72 hours, and one on the sixth day.
1	0·02	No symptoms; survived.

The certainly lethal dose appears to be about 0·045 milligramme per kilogram, though the number of animals is insufficient to make this quite certain. The tendency for the body weight to affect the result is shown in the group of eleven animals which received 0·03 milligramme per kilogram. Those which survived, weighed 1·46, 1·54 and 1·7 kilograms, average 1·56. One weighing 1·24 died on the sixth day. The weights of those dying on the third day were 1·48, 1·58 and 1·77 kilograms, average 1·61. Those dying on the second day weighed 1·63, 1·65, 1·74 and 1·9, average 1·73 kilograms.

Symptoms.

The symptoms following the injection in animals dying in twenty-three to thirty hours after a dose of 0·045 milligramme per kilogram are not very striking until about the twentieth hour. Up to this time the animals are abnormally quiet and have "gone off" their food. Their ears have lost their tone and flop over to one side and their body tone generally is poor. There is in some weakness of the hind limbs.

Two or three hours later the symptoms are much more striking; there is general muscular weakness, the head lolling over to one side. The animal is lying on its side and fine tremors of the musculature can often be felt. The animal frequently dies with terminal convulsions, the eyes staring, respiratory failure having induced asphyxia. In rabbits receiving a smaller dose, apart from anorexia and quietness, no symptoms whatever are noticeable till about the end of the second day. At this stage they present alternate phases of quiet and activity. In the quiet stage the head falls on one side or forwards. The animal sits hunched with its head low and its hindquarters raised or at a later stage may lie prone. There is loss of tone of the musculature and fine shivering movements. The coat is somewhat staring and there is often slight dyspnœa. The gait, if the animal can be induced to walk, is incoordinate and the movements of the limbs are slapping, due to the lack of tone. During the intervals of activity the animal exhibits quick incoordinate movements, raising itself up in a jerky fashion ("starting movements"). As the condition becomes more severe, it lies prone and the periods of activity become less frequent till death ensues, often following a period of spasmodic movement. Asphyxia doubtless plays some part in the production of these periods of activity. The eyes are prominent at death which usually occurs by respiratory failure. A noteworthy feature in those animals which survive, is the frequent occurrence of blindness in one or both eyes.

Post Mortem Findings.

There is usually some congestion of the vessels of the skin and subcutaneous tissues round the site of the injection. Almost invariably hæmorrhages of small size are present in the lungs, not infrequently in the thymus and occasionally in the testes. The blood is fluid in the heart and vessels. The clotting time determined immediately after death in animals dying in about twenty-four hours is normal or somewhat increased (five, seven, eight, ten and thirteen minutes). In females the uterus is generally congested. The liver and the small gut are sometimes congested and the latter is often filled with bile stained mucus. Hæmoglobinuria is almost invariable.

The subcutaneous-intravenous index is $\frac{0{\cdot}045}{0{\cdot}002}$ = 22·5, a figure which is higher in this species than in any other which I have examined.

Effects in Guinea-Pigs.

The Effect of Intravenous Injection.

The effect of intravenous injection of the venom in a concentration of 0·01 milligramme per cubic centimetre is seen in Table VI. The injections were made into the jugular vein under local cocaine anæsthesia. The animals used weighed from 200 to 300 grammes.

TABLE VI.

Effect of Intravenous Administration to Guinea-pigs.

Number of Animals.	Average Body Weight.	Dose in Milligramme per 100 Grammes.	Result.
2	223	0·002	Death in 55 minutes and in less than 17 hours.
2	235	0·001	Both died on the second day.
10	239	0·0009	One died in 5 minutes, seven in from 19 to 26 hours, and two in less than 42 hours.
2	233	0·0008	One died on the third day and one on the fourth day.
10	252	0·0007	One died in 15 minutes, one in 18 hours, one in 22 hours, four in less than 44 hours, one on the third day, and two on the eighth day.
12	226	0·0006	One died in 5 minutes, one in 9 minutes, one in 12 minutes, one died on the third day, and the remainder survived.

These results are of particular interest since only a few of the deaths appeared to be caused by intravascular clotting, the great majority being due apparently to the neurotoxic action of the venom.

In the animals which died within the first few minutes following the injection, the cause of death was thrombosis. Within one to two minutes they were profoundly collapsed and in some cases convulsed vigorously. The cornea was insensitive and the pupils dilated. In others profound shock dominated the picture.

Post Mortem Findings.

There was fibrin in the right auricle and ventricle, in some thrombosis in the lung vessels and in others patchy thrombosis in the portal venous system, with intense congestion of the spleen and small intestine in those surviving for ten to twenty minutes. Most of the other animals presented a primary shock evidently due to thrombosis with an onset within one or two minutes after the injection. They, however, appeared to recover from this within five to ten minutes and at a later stage symptoms appeared indistinguishable from those seen in animals injected with somewhat larger doses subcutaneously. There were paresis of the limbs, shivering and "starting movements," collapse and respiratory failure.

In some the paresis of the limbs and the quick jerking movements commenced within seven or eight minutes after the injection.

In animals dying at the end of the first day and later the lungs were the seat of extensive hæmorrhages and hæmoglobinuria was present in many. The adrenals were congested and in one or two there were small hæmorrhages in organs other than the lungs. There was neither portal congestion nor any macroscopic evidence of thrombosis and the blood was fluid. The clotting time was nine to ten minutes in the few which were examined immediately after death.

The certainly lethal dose by the intravenous route is about 0·0007 milligramme per hundred grammes or 0·007 milligramme per kilogram.

The Effect of Subcutaneous Injection.

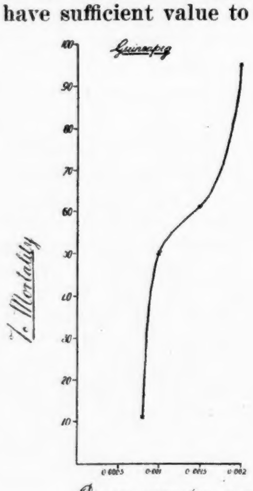
In some preliminary experiments I used animals ranging in weight between 250 and 300 grammes and the dosage was not calculated per hundred grammes weight of animal, though it is so expressed in Table VII, which indicates the approximate relation between size of dose and death time. The venom was injected in a concentration of two milligrammes per cubic centimetre for the larger doses and 0·4 milligramme per cubic centimetre for the smaller doses. In all cases the site of the injection was the subcutaneous tissue of the abdominal wall.

TABLE VII.

Effects of Varying Dose of Venom injected subcutaneously into Guinea-pigs

Number of Animals.	Dose.	Dose in Milligrammes per 100 Grammes.	Result.
1	4·0	1·2	Death in 15 minutes.
2	2·0	0·7	Death in 19 and 20 minutes.
1	1·0	0·38	Death in 30 minutes.
2	0·5	0·19	Death in 27 and 32 minutes.
6	0·2	0·07	Three died in less than 1 hour, one in 52 minutes, and two in 1 hour 15 minutes.
2	0·1	0·03	Death in 1 hour 20 minutes and in 1 hour 24 minutes.
2	0·06	0·018	Death in 1 hour 54 minutes and in 2 hours 5 minutes.
3	0·05	0·015–0·018	Death in from 2¼ to 4¼ hours.
2	0·04	0·012–0·013	Death in from 3 to 5 hours.
4	0·02	0·06	Death in from 8 to 19 hours.

The number of observations is far too small to plot a dose-death-time curve (Acton and Knowles[5]) since considerable variations in the death time occur with the smaller doses of venom. So wide in fact is the variation in time with this venom that it seems doubtful if such curves for any species have sufficient value to be worth the large expenditure of animals necessary. I have, however, determined the "characteristic" of the venom by subcutaneous injection into guinea-pigs varying in weight between 200 and 300 grammes. Table VIII gives in condensed form the data upon which Graph I is constructed, the percentage mortality being plotted against the dose. The sex of the animals used was fairly evenly distributed. The venom was administered in a concentration of 0·01 milligramme per cubic centimetre.



GRAPH I.
"Characteristic" for subcutaneous injection of tiger snake venom in guinea-pigs of about 250 grammes weight. Concentration of venom used—0·01 milligramme per cubic centimetre.

The effect of body weight was strikingly evident in these

TABLE VIII.

Data for "Characteristic" of Tiger Snake Venom injected subcutaneously in Guinea-pigs.

Number of Animals.	Average Body Weight in Grammes.	Dose in Milligramme per 100 Grammes.	Number of Deaths.	Mortality. %	Death Times.
20	260	0·002	19	95	Five on the first, eleven on the second, and three on the third day.
36	244	0·0015	22	61	Five on the first, four on the second, two on the third, four on the fourth, two on the fifth, four on the sixth, and one on the seventh day.
26	239	0·001	13	50	Two on the second, one on the fourth, three on the fifth, one on the sixth, three on the seventh, and three on the eighth day.
18	262	0·0008	2	11	One on the first and one on the fourth day.

observations. Analysis of the group of twenty-six animals which received 0·001 milligramme per hundred grammes, shows that there were thirteen whose weights exceeded the average. The average weight of these was 269 grammes and the mortality 77% (ten deaths). There were thirteen whose weights were below the average of the whole group with an average weight of 209 and mortality 23% (three deaths). A similar effect is evident in the analysis of the thirty-six guinea-pigs which received 0·0015 milligramme per hundred grammes. There were fifteen with body weights above the average weight for the whole group with an average weight of 273 and a mortality of 80% (twelve deaths) and twenty-one below the average body weight for the whole group with an average weight of 225 and a mortality of 48% (ten deaths).

For the determination of the characteristic (Graph I) the data given in Table VII would be more satisfactory if the average body weights of the two middle groups were somewhat higher. This would probably make the characteristic even steeper than it is.

The certainly lethal dose is about 0·002 milligramme per hundred grammes or 0·02 milligramme per kilogram for guinea-pigs of about 260 grammes in weight. The only animal which survived with this dose weighed 225 grammes. With larger animals the certainly lethal dose is definitely less.

This is well shown in Table IX in which are given the results of the subcutaneous injection of much heavier animals with 0·002, 0·0016 and 0·0014 milligramme per hundred grammes (the venom being used in a concentration of 0·01 milligramme per cubic centimetre). It will be observed that the death time is much shortened. Death was invariable even with the smallest dose used.

TABLE IX.

Effect of the Subcutaneous Injection of Venom in Guinea-pigs (400-550 Grammes).

Number of Animals.	Average Weight in Grammes.	Dose in Milligramme per 100 Grammes.	Average Death Time in Hours.
12	475	0·002	18
10	453	0·0018	18
6	456	0·0016	20¼
6	465	0·0014	25

I have made use of guinea-pigs to compare "primary" venom (that is venom collected at the first milking after capture) from snakes in good condition, with "primary" venom from reptiles in poor condition, heavily infested with fluke and starving and with the ordinary "pooled venom" as used throughout the experiments recorded in this paper, consisting of venom collected by milking on a number of occasions at monthly intervals subsequent to the first collection. For this purpose guinea-pigs varying in weight between 250 and 300 grammes were used and a dose of venom (in a concentration of 0·01 milligramme per cubic centimetre) irrespective of weight was given to each animal in each group of ten. The following results in Table X were obtained.

TABLE X.

Comparison of Primary, Primary Starved and Pooled Venom.

Venom.	Total Dose in Milligramme.	Number of Animals.	Average Body Weight.	Number of Deaths.	Average Time of Death.
"Primary" ..	0·004	10	279	8	Fourth day.
	0·003	10	255	2	Sixth day.
"Primary Starved"	0·005	10	267	6	Fourth day.
	0·004	10	270	5	Fifth day.
	0·003	5	270	2	Seventh day.
"Pooled Secondary"	0·005	10	296	10	Second day.
	0·004	10	263	7	Fifth day
	0·004	10	261	7	Sixth day.

These results which are only of a preliminary nature, suggest that while there is no significant difference observable between the effect of primary and pooled secondary venom, the "primary starved" venom is somewhat less potent. The venoms were all collected by Dr. N. H. Fairley by "milking" and the absence of significant difference in potency between primary and secondary pooled venoms speaks for the conditions under which the reptiles were kept at the Melbourne Zoological Gardens and for the care with which the milking was carried out. The starved reptiles, however, yielded a primary venom which appeared to be somewhat less potent, though more observations on larger numbers of animals of the same weight and with the same dosage would be necessary for decisive proof of this suggestive result.

Symptoms.

The symptoms which follow subcutaneous injection are very similar within the range of dosage employed. The animals first become quiet and "go off" their feed, their coats become staring and after

a variable time weakness and later definite paralysis of the hind limbs appear. "Starting movements" are very common, the animal squatting hunched up and suddenly projecting itself slightly upwards on all four feet. Periods in which these movements are very evident, alternate with periods of immobility. Towards the end which nearly always occurs with respiratory failure (the heart going on beating for some little time after the respirations have ceased), there is loss of tone and paralysis of the body musculature, the animal lying prone or on one side. The pupils at this stage are dilated. Animals killed rapidly with large doses do not show any hæmoglobinuria, but this is a constant feature in animals which die following injection of doses in the neighbourhood of the certainly lethal dose.

Animals which survive after receiving doses of venom which are just sublethal, are nearly always paralysed for some hours and it is noteworthy that in rabbits, guinea-pigs, rats and mice there is a high incidence of blindness in one or both eyes in the survivors. Other venoms, for example that of the copper-head (*Denisonia superba*), also cause prolonged periods of paralysis which may terminate favourably, but the survivors are never afflicted with blindness. The blindness is caused by opacities in the cornea and sometimes the anterior chamber appears to be affected. The phenomenon calls for further investigation, but is provisionally regarded as being due to the involvement of the fifth nerve and to injury while the cornea is more or less insensitive.

Post Mortem Findings.

In animals dying rapidly from large doses of venom there are only slight local signs at the site of injection, congestion and occasionally hæmorrhage. The lungs are congested, with hæmorrhages of varying size in their substance. Hæmorrhages, other than petechial, are rarely seen elsewhere. The blood is fluid and coagulation is delayed. The phrenic nerves are usually insensitive, the diaphragm failing to contract when they are electrically stimulated immediately after death, while the heart is still beating. Stimulation of the sciatic nerves at the same time yields good contraction of the muscles innervated by them. In none of the animals dying early is there any hæmoglobinuria.

In animals dying more slowly with doses in the neighbourhood of the certainly lethal dose, local lesions at the site of injection are also slight or absent. Hæmoglobinuria and hæmorrhages in the lungs are almost invariably present. The bowel often contains bile stained mucus and sometimes there is enteritis which may be hæmorrhagic. The adrenals are nearly always congested and sometimes contain gross hæmorrhages. The testis or uterus is frequently congested. The blood is fluid, no thrombi in the heart or vessels are obvious to the naked eye and the clotting time is somewhat delayed (eight, nine, ten, twelve, fifteen minutes).

The subcutaneous-intravenous index for the guinea-pig is $\frac{0{\cdot}002}{0{\cdot}0007} = 2{\cdot}9$.

EFFECTS IN THE RAT.

The rats used in these experiments were of various colours and were the progeny of some animals obtained from the Imperial Cancer Research Fund Laboratories.

Effects of Intravenous Injection.

In a few animals the venom was injected in a concentration of 0·02 milligramme per cubic centimetre by the tail vein. The results are summarized in Table XI.

TABLE XI.
Result of Intravenous Injections in Rats.

Number of Animals.	Average Weight in Grammes.	Dose in Milligramme per 100 Grammes.	Result.
4	134	0·007	One died in 38 minutes, one in less than 15 hours, one in 21 hours, and one in less than 48 hours.
2	122	0·006	Both died in less than 48 hours.
1	132	0·005	Severe symptoms; recovery
1	158	0·004	Severe symptoms; recovery.

The symptoms in animals which received a fatal dose were fairly uniform. During the first minute after the injection they ran round their cage in an excited manner. Shortly after they became dyspnœic and within four or five minutes collapsed with definite paresis of the hind limbs and obvious dyspnœa. They remained prone or lay on one side for a variable period and except one animal which died after thirty-eight minutes, within ten to twenty minutes recovered from these early severe symptoms to die later with symptoms like those seen in animals injected with somewhat larger doses subcutaneously. One or two animals which died, presented only slight dyspnœa and no collapse in the first few minutes after injection. Some of the rats which recovered, presented early symptoms from which they recovered in a few minutes. These, though next day they appeared somewhat ill, presented no striking late symptoms.

Post Mortem Findings.

In the rat which died in thirty-eight minutes there were thrombi in the right auricle and ventricle, in the lung vessels and in the portal veins. The spleen was enlarged and the small intestine was intensely congested. In another rat which died in less than fifteen hours, there were hæmoglobinuria and hæmorrhages in the lungs. The upper part of the small intestine was filled with bile stained mucus and an area five centimetres in length in the ileum was intensely congested and hæmorrhagic as a result of thrombosis in one of the smaller mesenteric veins. The spleen was not noticeably enlarged. In the animals which died before the

end of the second day, there were hæmoglobinuria and hæmorrhages in the lungs and the small intestine contained much bile stained mucus.

The certainly lethal dose by the intravenous route for rats of about 130 grammes is 0·007 per hundred grammes or 0·07 milligramme per kilogram.

Effects of Subcutaneous Injection in the Rat.

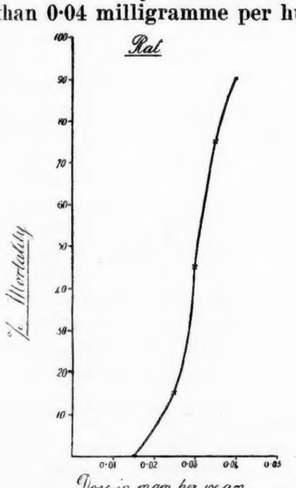
A large number of animals was used to determine the "characteristic" of the venom by subcutaneous injection (Graph II). The venom was administered in a concentration of 0·01 milligramme per cubic centimetre in the subcutaneous tissue of the thigh. The results are shown in Table XII.

TABLE XII.
Data for the "Characteristic" of the Venom in Rats.

Number of Animals.	Average Weight in Grammes.	Dose in Milligramme per 100 Grammes.	Number of Deaths.	Mortality. %	Death Time.
20	124	0·04	18	90	Ten died on the first, one on the second, three on the third, three on the fourth, and one on the seventh day.
20	132	0·035	15	75	Four died on the second, seven on the third, three on the fourth, and one on the 15th day.
20	141	0·030	9	45	Two died on the second, four on the third, two on the fourth, and one on the tenth day.
20	125	0·025	3	15	One died on the third, one on the fifth, and one on the ninth day.
20	135	0·015	0	0	—

The certainly lethal dose is evidently a little more than 0·04 milligramme per hundred grammes or 0·4 milligramme per kilogram for rats of about 125 grammes. The subcutaneous-intravenous index is therefore rather more than

$$\frac{0{\cdot}04}{0{\cdot}007} = 5{\cdot}7.$$



GRAPH II.
"Characteristic" for subcutaneous injection of tiger snake venom in rats of about 125 grammes weight. Concentration of venom used—0·01 milligramme per cubic centimetre.

The relation of dosage to death time was observed in animals of 170 to 240 grammes weight (Table XIII), animals of nearly the same weight being used for each dose. Much of the variation observed in death time is due to inequalities in body weight. The venom was used in concentrations of 5·0 milligrammes per cubic centimetre, 1·0 milligramme per cubic centimetre and 0·1 milligramme per cubic centimetre.

TABLE XIII.
Relation of Dosage to Death Time.

Number of Animals.	Average Weight in Grammes	Dose in Milligrammes.	Death Time.
2	234	5·0	34 minutes.
2	200	2·0	40 minutes.
4	191	1·0	71 to 90 minutes (average, 80·5 minutes).
2	207	0·5	78 minutes.
2	200	0·25	168 and 228 minutes.
2	183	0·2	132 and 146 minutes.
3	176	0·1	250, 260 and 279 minutes (average, 263 minutes).
2	215	0·1	330 minutes and 12 hours.
2	170	0·05	54 hours.
2	200	0·025	One survived and one died on the eighth day.

The symptoms and *post mortem* changes are fairly uniform whether a large or a small dose be employed. Occasionally with large subcutaneous doses death appears to be due to thrombosis (C. J. Martin,[1] Martin and Lamb[6]).

At a varying period after the injection the animal looks sick, the coat is staring and there is dyspnœa. Paresis of the hind limbs comes on early, shortly followed by paresis of the fore limbs and body musculature generally. At this stage there is salivation due either to increased secretion or to paralysis of the swallowing mechanism. The respirations are audible and laboured. The pupils in the earlier stages are contracted, but later with the onset of asphyxia are dilated and more or less cyanosis is present. Collapse is a noteworthy feature in the later stage and there are occasional "starting movements." Hæmoglobinuria is almost constant in deaths taking place after the first hour. In later deaths hæmorrhage from the conjunctiva and blindness associated with corneal injury are frequent signs. Death usually occurs from respiratory failure.

Post Mortem Findings.

Stimulation of the phrenic nerves generally caused fairly brisk diaphragmatic contraction when carried out immediately after death. The coagulation of the blood is delayed. There may be weak clotting after three or five minutes or no clotting after eighteen to twenty minutes.

There are hæmorrhages in the lungs, massive or petechial. In the thymus, adrenals and in the nail beds petechial hæmorrhages are common. Occasionally they occur in the peritoneal surface of the bowel. The small intestine usually contains bile stained mucus, but sometimes is intensely congested. In one or two animals which died early after larger doses, though no obvious thrombi were found, it seemed likely from the appearance of the intestine that patchy thrombosis in the portal system had occurred. In these there were no other obvious lesions.

The local lesions at the site of the injection are slight. Congestion and œdema are sometimes, but

not invariably present and hæmorrhage is rare. Hæmoglobinuria is frequent, but no hæmolysis can be demonstrated in the shed blood.

EFFECTS IN THE MOUSE.

The mice used were partly albinos bred from an original pair obtained from Professor Brailsford Robertson and partly coloured strains bred from mice obtained from the Imperial Cancer Research Fund Laboratories.

The Effects of Intravenous Injections.

The results of intravenous injection into the tail vein of venom in a concentration of 0·05 and 0·01 milligramme per cubic centimetre are set out in Table XIV. The mice used weighed from fifteen to twenty-four grammes.

TABLE XIV.
Results of Intravenous Injection in Mice.

Number of Animals.	Weight or Average Weight.	Dose in Milligramme per 20 Grammes.	Result.
1	25	0·01	Death in 3 minutes.
1	15	0·008	Death in 3 minutes.
1	22	0·005	Death in 5 minutes.
4	19	0·003	Death in 1½, 3, 9 minutes, and in 3 hours 18 minutes.
4	16	0·002	Death in 30 minutes, in 2 hours, 2 hours 45 minutes, and in 4 hours 53 minutes.
3	20	0·001	Two died in 2 minutes and one in 4 minutes.
4	19	0·0008	One died in 3 minutes, one in 1 hour 27 minutes, and the others on the second day.
2	21	0·0005	One died in 46 hours and one survived.

The mice which died rapidly, collapsed almost immediately after the injection, gave a few convulsive kicks and lay prone or on one side with severe dyspnœa.

Post Mortem Findings.

Post mortem there was invariably thrombosis more or less extensive in the vascular system. In the more extreme cases there was clotting in the portal veins and in the inferior *vena cava* and right side of the heart.

The animals which died in from thirty minutes to four hours, developed initial symptoms similar to those observed in other species and remained collapsed till death ensued. In these there was invariably patchy thrombosis in the portal veins with hæmorrhages and œdema of the small bowel and enlarged spleen. In several of these there were hæmoglobinuria and hæmorrhages in the lungs.

The certainly lethal dose by the intravenous route appears to be about 0·0008 milligramme per 20 grammes or 0·04 milligramme per kilogram, though the number of observations is too small for its certain determination.

The Effects of Subcutaneous Injections.

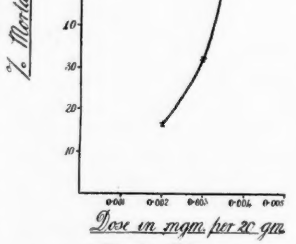
A large number of animals was injected with venom in the subcutaneous tissue of the thigh to determine the "characteristic" of the venom for this species. The results are recorded in Table XV and Graph III. The venom was injected in a concentration of 0·01 milligramme per cubic centimetre and the animals varied in weight from fourteen to twenty-five grammes.

TABLE XV.
Results of Subcutaneous Injections in Mice.

Number of Animals.	Average Weight in Grammes.	Dose in Milligramme per 20 Grammes.	Number of Deaths.	Mortality. %	Death Time.
19	20	0·005	15	79	Three in 17 hours, one in 19 hours, one in 20 hours, two in 24 hours, and eight in 40 hours.
30	18	0·004	19	63	Five in 22 hours, three in 25 hours, ten in 45 hours, and one in 52 hours (one on twelfth day not included).
22	19·6	0·003	7	32	One in 17 hours, one in 20 hours, four in 40 hours, and one in 72 hours.
30	21	0·002	5	16·6	Three on fifth, one on sixth, and one on the eighth day.

Owing to the irregular way in which these small animals die without obvious cause, it might have been better to exclude all deaths occurring after the third day, but experience with other species points to the occurrence of late deaths of the individuals with doses somewhat below the certainly lethal dose. The certainly lethal dose for this species is more than 0·005 milligramme per 20 grammes or 0·25 milligramme per kilogram and the subcutaneous-intravenous index more than $\frac{0{\cdot}005}{0{\cdot}0008} = 6{\cdot}25$.

In the animals which received 0·005 milligramme per 20 grammes the symptoms were fully developed after ten or twelve hours. There was paralysis of the hind limbs and many were collapsed with dyspnœa and obvious general weakness. In the animals of the third group, after eighteen hours six were paralysed in the hind limbs and the remainder had no symptoms then or later.



GRAPH III.
"Characteristic" for subcutaneous injection of tiger snake venom in mice of about 20 grammes weight. Concentration of venom used—0·01 milligramme per cubic centimetre.

Post Mortem Findings.

There were no obvious lesions at the site of injection. Hæmorrhage in the lungs was almost invariable and hæmoglobinuria was sometimes present. The

small intestine was usually distended with bile stained mucus and a few animals presented a hæmorrhagic condition of the small intestine which suggested the presence of portal thrombi. Martin[1] in his work on black snake venom draws attention to the possibility that many of the larger lung hæmorrhages are due to thrombosis, so that it is possible that in this as in other species the active principle which causes coagulation of the blood, may play a part in causing death even when the venom is injected subcutaneously.

The incidence of blindness in the survivors of these experiments is a further point of some interest. Of the four mice which survived the injection of 0·005 milligramme per 20 grammes, one was blind in both eyes and of the eleven survivors which had received 0·004 milligramme per 20 grammes, eight were blind in one or both eyes. One of each of the other two larger groups of survivors which had received 0·003 and 0·002 milligramme per 20 grammes, was blind.

To summarize the results obtained in these various species the certainly lethal dose estimated per kilogram of body weight by subcutaneous and intravenous injection is presented in Table XVI. Where the result is only approximate owing to the small number of observations, the figure is marked with an asterisk.

TABLE XVI.

Certainly Lethal Dose of the Venom of Notechis scutatus.

Species.	Subcutaneous in Milligramme per Kilogram.	Intravenous in Milligramme per Kilogram.	Subcutaneous-intravenous Index.
Horse	0·005*	—	—
Sheep (Fairley) ..	0·01	—	—
Goat (Fairley) ..	0·018	—	—
Monkey	0·02*	—	—
Cat	about 0·10	—	—
Rabbit	0·045*	0·002	22·5
Guinea-pig	0·02	0·007	2·9
Rat	more than 0·40	0·07*	more than 5·7
Mouse	more than 0·25	0·04*	more than 6·2

The susceptibility of any species to the action of this venom appears to depend to a large extent on the body weight, though the cat and rat are more resistant and the guinea-pig is more susceptible than they should be if weight alone determined susceptibility. The rule which I have shown to apply in this venom in regard to large and small individuals of a species illustrated by observations on the guinea-pig, may also be applied to the species themselves. This does not appear to be the case with other venoms. The observations of Acton and Knowles[5] on cobra (*Naia tripudians*) venom give the certainly lethal dosage injected subcutaneously, recalculated for this purpose in milligramme per kilogram, as horse 0·05, monkey 1·0, dog 1·0, rabbit 0·25, guinea-pig 0·33, rat 0·8 and mouse 0·12 milligramme. With this venom the larger animals except the horse appear to be less susceptible than the smaller, though the rat is, as in the case with tiger snake venom, unduly resistant and the rabbit unduly susceptible. Observations on the venom of the common krait (*Bungarus candidus*) by the same authors give values for subcutaneous injection of 0·06 for the monkey, 0·1 for the rabbit, 1·0 for the guinea-pig and 1·3 for the rat, a series which is even more regular than my tiger snake figures and suggest that with increasing body weight in different species there is increasing susceptibility to the action of this venom. For *Vipera russelli* the figures of Acton and Knowles are 3·1 milligrammes for the monkey and 1·66 for the guinea-pig and rat. My own incomplete observations on the venoms of other Australian colubrides also do not resemble the series obtained with tiger snake venom. For *Pseudechis guttatus* the subcutaneous certainly lethal dose is much the same (between 0·6 and 0·8 milligramme) for the rabbit, guinea-pig and rat. For death adder (*Ancanthophis antarcticus*) the figures are for sheep 0·25 milligramme (Fairley), rabbits 0·15 milligramme and guinea-pig 0·15 milligramme. For copper-head venom (*Denisonia superba*) they are sheep 0·1 milligramme (Fairley), rabbit 0·7 milligramme, guinea-pig 0·06 milligramme, rat 1·4 milligrammes and mouse 1·2 milligrammes per kilogram. Despite the fact that with other venoms, with the exception of the krait, species variation in susceptibility appears to outweigh any difference dependent on body weight, the rule appears to hold in the main for the venom of the tiger snake, though, as pointed out above, species differences appear in the case of the cat, rat and guinea-pig. The uniformity of symptoms with tiger snake venom (death being almost invariably due to the action of neurotoxic constituents) and the comparatively slight variation in gross *post mortem* findings in different species, make it easier to argue from these results. It is true that there are obvious species differences in hæmolytic activity, the rat, rabbit and guinea-pig being more susceptible than the horse, cat and monkey as judged by the incidence of hæmoglobinuria. These are possibly explained by *in vitro* differences in susceptibility of the red blood corpuscles of hæmolysis by the venom. With cobra venom Kyes and Sachs[7] found that the red blood corpuscles of the guinea-pig and rat were much more susceptible and those of the rabbit somewhat more so than those of the horse. There are also species differences in regard to the activity of the thrombase of tiger snake venom which are well shown by the subcutaneous-intravenous indices for the sheep 2·0 (Fairley), for the rabbit 22·5, for the guinea-pig 2·9, for the rat rather more than 5·7 and for the mouse more than 6·2.

Despite these two striking differences in the activity of the venom in different species we may confidently place the certainly lethal dose for man in the range of the observed certainly lethal doses of the species examined. In the absence of evidence that man exhibits undue susceptibility or resistance to the action of the venom, it seems probable that

the certainly lethal dose per kilogram lies between 0·005 and 0·1 milligramme, the doses for the horse and sheep respectively.

The choice of the sheep and goat by my colleague Fairley for his comparison of the toxicity of the venom of the Australian colubrides is therefore justified as far as this venom is concerned by the probability that an animal of this size will yield a first approximation to the lethal dosage in man.

CONCLUSIONS.

1. A study of the certainly lethal dose of this venom in the horse, monkey, cat, rabbit, guinea-pig, rat and mouse, while it emphasizes species differences in hæmolytic and thrombotic effects, displays general uniformity of symptoms and also of gross *post mortem* findings, death being due to neurotoxic constituents in the venom.

2. The body weight of individuals in a species influences the certainly lethal dose, heavier individuals being more susceptible to the action of this venom. This in general outweighs individual differences in susceptibility.

3. The lethal doses for the species studied suggest that average body weight of animals plays a part in determining sensitiveness of different species for this venom, which are in general not outweighed by individual species susceptibility.

4. This last rule does not appear to apply for the venoms of other Australian colubrides nor for that of the cobra.

5. Reasons are advanced for regarding the certainly lethal dose for man as being of the order of 0·005 to 0·01 milligramme per kilogram.

6. Preliminary evidence is brought forward that the pooled tiger snake venom used in these experiments is not less potent than the venom first collected from the snakes when captured. If the snakes are in bad condition this primary venom may be less potent than that from snakes captured in good condition.

7. The incidence of blindness in animals recovering from sublethal doses of venom is a noteworthy feature.

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A PRELIMINARY NOTE ON THE VENOM OF THE AUSTRALIAN COPPER-HEAD (*DENISONIA SUPERBA*): ITS TOXIC EFFECTS IN THE COMMON LABORATORY ANIMALS.[1]

By C. H. KELLAWAY, M.C., M.D., M.S., M.R.C.P.,
(*From the Walter and Eliza Hall Institute, Melbourne.*)

THE venom of the copper-head (*Denisonia superba*) does not appear to have been studied previously. Like that of the other Australian colubrides, it causes hæmorrhages in various organs and hæmolysis and in general death results from its neurotoxic action. Though in some animals it causes delay in the coagulation of the blood, it does not cause thrombosis when injected intravenously.

In the present paper the certainly lethal dose has been determined for the common laboratory animals as a necessary preliminary to further studies on the toxicology of the venom.

EFFECTS IN THE HORSE.

Three horses were injected with varying doses of this venom in a concentration of six milligrammes per cubic centimetre. The injections were made subcutaneously in the tissues of the neck. The results are shown in Table I.

TABLE I.
The Effect of Subcutaneous Injections in Horses.

Weight in Kilograms.	Sex.	Dose in Milligramme per Kilogram.	Result.
344·3	Gelding	0·1	Paralysed in 6½ hours and died in 11 hours.
346	Gelding	0·05	Paralysed in between 12 and 14 hours and died in 17 hours.
349	Mare	0·02	Paralysed in 17 hours and died in between 33 and 37 hours.

It will be seen that the horse is very susceptible and that the certainly lethal dose is in all probability not less than 0·02 milligramme per kilogram, though the number of animals is sufficient only to indicate the toxicity of the venom.

Symptoms.

The picture presented by these animals was somewhat different from that seen after the injection of the venom of the tiger snake. Within a few hours of the injection they became drowsy and a certain stiffness of the limbs was noted. In from six to seventeen hours they became paralysed and were unable to rise. The march of the paralysis was not observed, save that the neck and abdominal muscles and the diaphragm appeared to be involved last of all. The breathing, when the animals were "down," was purely diaphragmatic, but was not obviously dyspnœic, though œdema of the lungs was found in two at autopsy.

In horses poisoned with the venom of *Notechis scutatus* the facial muscles are very irritable and

[1] This research was carried out under a grant from the Commonwealth Government Department of Health.

a slight tap on the skin over them causes retraction of the angle of the mouth. The facial muscles also contract with every inspiration. This is not the case following the injection of the venom of the copper-head and the paralysis is much quieter, though the animal may make repeated efforts to get up. There is also no excessive sweating nor is salivation a prominent feature as after the injection of tiger snake venom. During the paralytic stage the pupils are dilated, but the corneal reflex remains active until very late.

Post Mortem Findings.

There was blood-stained œdema of the subcutaneous tissues of the neck extending from the site of the injection to the middle line. The fat in two of the animals appeared to be somewhat jaundiced and yellow-stained fluid was present in the pericardium. There were petechial hæmorrhages in the pericardial fat and in two of the horses in the heart muscle itself, particularly in that of the right ventricle. There was slight staining of the intima of the aorta. The blood was clotted in the heart and great vessels in the first animal, in which the autopsy was made eight hours after death, but was fluid in the great veins in the other two examined three and six hours after death. The lungs were congested but not œdematous in the animal which received 0·05 milligramme per kilogram, but there were many small submucosal hæmorrhages in the trachea and larger bronchi. In the other two animals there were much congestion and œdema of the lungs with yellow stained frothy fluid in the trachea and bronchi. The adrenals in the animal which lived longest, were intensely hæmorrhagic and in one of the others they were less severely affected. In none of these horses had the spleen the "black-currant jam" appearance seen after the injection of tiger snake venom. There were petechial hæmorrhages in various organs, in the subperitoneal coat of the large bowel, in the pancreas and in the mesenteric fat. The liver and pancreas were congested and the kidneys intensely so, the glomeruli being obvious to the naked eye. All these animals had intense hæmoglobinuria and in two, in which the urine was examined microscopically after centrifuging, there were neither red blood cells nor "ghosts." The bladder mucosa was congested and in one animal there were numerous submucosal petechiæ.

EFFECTS IN THE CAT.

The cat is moderately resistant to the action of the poison. Table II shows the results of subcutaneous injection in a small series of animals. The venom was injected into the abdominal wall in a concentration of 2·0 milligrammes per cubic centimetre.

The certainly lethal dose is probably about 1·2 milligrammes per kilogram.

The Symptoms.

A striking feature of the action of this venom is the rapidity of onset and the extent of the paralysis in animals receiving definitely sublethal doses of venom. The earliest symptoms, apart from anorexia, are loss of tone and power of the body musculature, noticeable first in the limbs and later in the trunk and neck muscles. Dyspnœa was not observed in any of these animals and the "quiet" nature of the paralysis is very characteristic, "starting movements" being absent. The colour is generally good and the pupils of moderate size till quite late in the picture. The most extreme degrees of paralysis may be observed for from one to three days with ultimate complete and dramatic recovery. The animal which died on the sixth day, seemed likely to recover after three days, but remained paralysed with final respiratory failure. There were terminal asphyxial convulsions greatly modified by the extent of the paralysis.

TABLE II.
Results of Subcutaneous Injection in Cats.

Weight in Kilograms.	Sex.	Dose in Milligrammes per Kilogram.	Result.
2·0	Female	1·5	Paralysed in 6 hours; dead in less than 15 hours.
2·2	Male	1·2	Dead in less than 18 hours.
3·26	Male	1·0	Paralysed in 15 hours; recovered after 72 hours.
2·78	Male	0·8	Paralysed in 15 hours; died on the sixth day.
2·4	Female	0·6	Paralysed in 15 hours; complete recovery in 60 hours.

Post Mortem Findings.

In the three animals which died, there were petechial hæmorrhages in the thymus and a few small hæmorrhages in the lungs, but no hæmoglobinuria. The blood was fluid and coagulation was not delayed (six minutes).

EFFECTS IN THE RABBIT.

The results of intravenous injections are recorded in Table III. The venom was administered in a concentration of 2·0 milligrammes per cubic centimetre into a marginal ear vein.

TABLE III.
Results of Intravenous Injection in Rabbits.

Number of Animals	Average Weight in Kilograms.	Dose in Milligramme per Kilogram.	Result.
2	1·77	1·0	One died in 17 minutes and one in 19 minutes.
2	1·78	0·8	One died in 7 minutes and one in 16 minutes.
2	1·94	0·6	One died in 26 minutes and one in 1 hour 52 minutes
4	1·64	0·4	One died in 57 minutes, one in 1 hour 5 minutes, one in 2 hours 10 minutes, and one in less than 18 hours.
4	1·61	0·3	One died in 1 hour 50 minutes one in between 3 and 5 hours, one in less than 18 hours, and one at the end of the second day.
2	1·40	0·2	One only showed slight weakness of the hind limbs and ataxia; it recovered completely in 36 hours.

The certainly lethal dose is 0·3 milligramme per kilogram.

The Symptoms.

In the animals which die rapidly, the first symptom noted is that the head falls over on one side; a rapid, quiet loss of tone follows and the animal falls on one side. Death appears to result from respiratory failure, convulsions being masked by the paralysis, though a few convulsive kicks sometimes occur immediately preceding death. In the animals dying in the course of an hour or so, the earliest symptoms noted were weakness and loss of tone in the limbs. During the ensuing twenty minutes the paralysis became more extensive and death ensued from respiratory failure. In some animals there were a few convulsive kicks shortly before death. The pupils were contracted except terminally, when dilatation was sometimes observed. In the rabbit which died at the end of the second day, weakness and loss of tone in the limbs were noted after five and a half hours. By the seventeenth hour paralysis was complete except for the muscles of respiration. In the early stages there was some diarrhœa and before paralysis became complete a few "starting movements" were observed. Later the paralysis was "quiet" and the respirations were regular and apparently normal until near the end.

Post Mortem Findings.

In the animals which died rapidly, the heart was usually found beating for some time after the respirations had ceased. In one or two electrical stimulation of the phrenic nerves immediately after death caused no contraction of the diaphragm, but stimulation of the sciatics immediately afterwards caused only a feeble response of the muscles innervated by them. In no case was any clotting observed in the heart or great vessels and injection was never followed by immediate shock as in animals in which intravascular thrombosis follows the injection of, for example, tiger or black snake venom. In rabbits which died within a few minutes, there were few changes observed at autopsy. In one the blood clotted extremely slowly (two hours). In animals dying in one to two hours hæmoglobinuria was present; there was well marked staining of the abdominal walls with blood pigment and blood stained fluid free in the peritoneal cavity. The lungs were congested. The blood was fluid; there were no clots and the coagulation time was delayed (twelve minutes). In the animal which died in from three to five hours, there was clot in the right side of the heart and portal vein and congestion of the small intestine and spleen. There were small hæmorrhages in the lungs and intense hæmoglobinuria. This was the only animal in which clotting was observed in the heart and vessels. The autopsy in this case was, however, made after the onset of *rigor mortis*.

The results of the subcutaneous injection of this venom are shown in Table IV, the venom being administered in the tissues of the abdominal wall in a concentration of 2·0 milligrammes per cubic centimetre.

TABLE IV.
The Results of Subcutaneous Injection in Rabbits.

Number of Animals.	Average Weight in Kilograms	Dose in Milligramme per Kilogram.	Result.
6	1·66	0·7	One died in less than 18 hours, two in 25 hours, one in less than 42 hours, one on the third day, and one was still paralysed on the fourth day but had recovered by the fifth day.
8	1·48	0·6	Three died in 16 hours, one in 24 hours, one in 48 hours, and three had severe symptoms but had recovered by the third day.
6	1·35	0·5	One died in 16 hours, three had severe symptoms but had recovered by the second day, and two had no obvious symptoms.
2	1·75	0·4	No symptoms.

The certainly lethal dose is about 0·7 milligramme per kilogram.

Symptoms.

The symptoms were similar to those observed in rabbits injected intravenously, but were slower in onset. In those animals which had severe symptoms, a quiet paralysis accompanied by profound loss of tone of the skeletal musculature was noted in sixteen hours. Dyspnœa was generally absent. The limb muscles were usually first involved, then the trunk muscles and finally those of the neck. The pupils were normal or slightly dilated. The animals lay flat out on the side or prone and no "starting movements" were observed. In animals which received smaller doses, ataxic gait and weakness of the hind limbs persisting for a variable period were the only symptoms.

Post Mortem Findings.

Hæmoglobinuria of severe or moderate degree was present in most of the animals which died. The peritoneal surface of the abdominal wall was stained with blood pigment. There was little change at the site of injection beyond a slight œdema of the surrounding subcutaneous tissues. The pleura and peritoneum contained free fluid in some animals. There were petechial hæmorrhages in the thymus and occasionally in the adrenals. The lungs were congested and petechial hæmorrhages were present. In nearly all the animals there was excess of bile stained mucus in the small intestine and in one there was congestion and hæmorrhage in the spleen. The blood was fluid and the coagulation time delayed (six and a half minutes in one animal and ten minutes in two others).

EFFECTS IN THE GUINEA-PIG.

The results of injection into the jugular vein under cocaine anæsthesia are shown in Table V. The venom was introduced (except in the case of the two largest doses) in concentrations of 0·02 and 0·01 milligramme per cubic centimetre. The animals were all females.

TABLE V.
Effect of Intravenous Injection in Guinea-pigs.

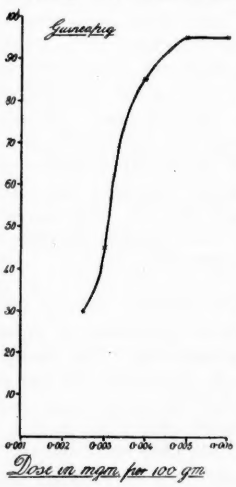
Weight in Grammes.	Dose in Milligramme per 100 Grammes.	Result.
250	0·2	Death in 7 minutes.
250	0·05	Death in 1 hour.
260	0·007	Death in 5½ hours.
285	0·007	
255	0·005	Death in 7 hours.
267	0·005	Death in 5¾ hours.
254	0·0035	Death in 8¼ hours.
272	0·0035	
269	0·003	Death in less than 16 hours.
257	0·003	
260	0·0025	Death in less than 16 hours.
263	0·0025	
268	0·0015	Death on the second day.
262	0·0015	
252	0·0012	Severe symptoms for 2 days, but survived.
260	0·0012	
255	0·001	No symptoms.
253	0·001	

The certainly lethal dose is about 0·0015 milligramme per hundred grammes or 0·015 per kilogram.

Symptoms.

The symptoms with larger doses were ushered in with a brief period of hyperactivity; there was some dyspnœa and then widespread paralysis rapidly ensued, death resulting from failure of respiration.

The animals which died in from five and a half to sixteen hours after the injection, showed definite weakness of the hind limbs in from two to four hours and in from four to eight hours were paralysed more or less completely. They lay prone with occasional "starting movements" and in many cases were somewhat dyspnœic. Those animals which received a sublethal dose showed weakness of the hind limbs and ataxia after eight hours and during the next twenty-four hours their symptoms appeared to increase in severity. They had, however, recovered by the end of the second day.



GRAPH I.
"Characteristic" for the venom of *Denisonia superba* in the guinea-pig. The venom was injected subcutaneously in a concentration of 0·02 milligramme per cubic centimetre.

Post Mortem Findings.

There was no obvious thrombosis in the heart or great vessels of any of these animals nor was there any indication of portal thrombosis, congestion of the intestines and splenic enlargement being absent. Hæmoglobinuria was not observed either during life or, since the bladder was invariably empty, at autopsy. There were hæmorrhages in the lungs and excess of bile stained mucus in the small intestine, but no other noteworthy changes.

The effects of the injection of venom into the subcutaneous tissue of the abdominal wall are seen in Table VI and Graph I. In Graph I the "characteristic" of this venom is seen and in Table VI the data from which it is constructed, are presented. The venom was injected in a concentration of 0·02 milligramme per cubic centimetre.

TABLE VI.
Effects of Subcutaneous Injection in Guinea-pigs.

Number of Animals.	Average Weight in Grammes.	Dose in Milligramme per 100 Grammes.	Mortality. %	Result.
20	275	0·006	95	Thirteen died in less than 17½ hours, three in 17¾ hours, one in 19 hours, one in 21 hours, one in 22 hours, and one survived.
20	268	0·005	95	Eleven died in less than 18 hours, two in 18 hours, two in 18½ hours, one in 19¼ hours, one in 20 hours, one in 22 hours, one in 24 hours, and one survived.
20	257	0·004	85	Three died in less than 18 hours, two in 18 hours, two in 19 hours, four in 20 hours, one in 22 hours, three on the second day, one on the third day, one on the fourth day, and three survived.
20	252	0·003	45	Seven died on the first day, two on the second day, and eleven survived.
20	257	0·0025	30	One died on the first day, four on the second day, one on the fourth day, and fourteen survived.

The certainly lethal dose is rather more than 0·006 milligramme per hundred grammes or 0·06 milligramme per kilogram.

Symptoms.

When doses of this order are administered, in from twelve to sixteen hours most of the animals are prostrate, lying prone or on their side with occasional kicking movements. There are sometimes involuntary movements of the head, neck and ears. Slight stimulation evokes a generalized muscular response which becomes less easily elicited as the paralysis becomes more profound. The pupil reflex is active in the early stages and the pupils widely dilated. The heart action is good and there is no cyanosis till late in the picture, when the respirations become slow and the heart beat feeble. Death usually takes place from respiratory failure, but the body is often cold and as in other species of animals, circulatory failure doubtless plays an important part in causing a fatal result.

Post Mortem Findings.

The blood is fluid at death and there are no obvious clots in the heart or great vessels. The clotting time is sometimes increased (3, 5, 6, 7, 7, 8, 8, 9, 9, 10, 11 and 14 minutes in a number of observations). At the site of injection there is usually no obvious local lesion, though occasionally there is slight congestion and even hæmorrhage.

The lungs are invariably congested with frequent petechial or massive hæmorrhages in their substance. The adrenals and in the female the uterus and in the male the testes are congested. The small intestine is also frequently congested and occasionally there are hæmorrhages into the wall and lumen. Less frequently there are hæmorrhages in the body musculature. Hæmoglobinuria was rarely observed in this species.

Stimulation of the phrenic nerves immediately after respiration had ceased, while the heart was still beating, usually caused contraction of the diaphragm. In three animals diaphragmatic contraction was not caused, though the muscles of the hind limb contracted vigorously when the sciatic was stimulated immediately afterwards.

Effects in the Rat.

Intravenous injections into the tail vein were made in a few animals. The results, after the use of venom in a concentration of 0·2 milligramme per cubic centimetre, are shown in Table VII.

TABLE VII.
Results of Intravenous Injection in Rats.

Number of Animals.	Weight or Average Weight in Grammes.	Dose in Milligramme per 100 Grammes.	Result.
1	94	0·14	Death in 48 minutes.
1	132	0·12	Death in 23 minutes.
2	114	0·1	Death in 1 hour and in less than 17 hours.
5	159	0·09	One died in 52 minutes, three in between 7 and 17 hours, and one survived.
3	127	0·07	One died in 3 hours, one in less than 11 hours, and one in 19 hours.
4	146	0·05	Two died in less than 11 hours and two survived.

The certainly lethal dose for rats of 160 grammes is probably about 0·09 milligramme per hundred grammes or 0·9 milligramme per kilogram.

These results are not very satisfactory, since there was too much variation in the weights of the animals used (96 to 217 grammes). Rats weighing 217 and 159 grammes died following the injection of 0·05 milligramme of the venom per hundred grammes, while animals weighing 112 and 100 grammes survived. Similarly the only animal which survived a dose of 0·09 milligramme, weighed 109 grammes.

Symptoms.

The symptoms presented by these animals were indistinguishable from those, presently to be described, in rats injected subcutaneously with this venom. The injections had no immediate effect. Paralysis appeared after a variable time and death occurred from respiratory failure, the heart continuing to beat for some time after respiration had ceased.

Post Mortem Findings.

There were no gross lesions in any of the organs. The heart and great vessels were free from clot and there was no congestion of the bowel or enlargement of the spleen. The clotting time in two observations was three and a half and four and a half minutes.

The results of subcutaneous injection in the rat are summarized in Table VIII. The injections were made into the tissues of the left thigh using venom in a concentration of 0·2 milligramme per cubic centimetre.

TABLE VIII.
Results of Subcutaneous Injection in Rats.

Number of Animals.	Average Weight in Grammes.	Dose in Milligramme per 100 Grammes.	Result.
10	138	0·14	Six died in less than 16 hours, two in 18 hours, one in 28 hours, and one survived.
10	143	0·12	Four died in less than 16 hours, one in 20 hours, one in 24 hours, and four survived.
10	141	0·10	Two died in less than 16 hours, one in 19 hours, and seven survived.
10	137	0·08	Very slight symptoms; all survived.

The certainly lethal dose is probably somewhat more than 0·14 milligramme per hundred grammes or 1·4 milligramme per kilogram of body weight. The numbers are too small to characterize the venom for this species.

Symptoms.

The earliest symptom observed was weakness in the hind limbs. The paralysis progressed till all the skeletal musculature was affected, with well marked loss of tone. With the larger doses there was some respiratory distress, the respirations being audible and fremitus could be felt on placing the hand on the chest wall. The mouth was wet either with saliva or with mucus from the respiratory passages. In a few animals the conjunctiva appeared to be irritated and there was excess of tears. Hæmoglobinuria was frequent and sometimes very intense. With the smallest dose very slight symptoms were observed. During the first day there was some weakness and loss of tone, but within twenty-four hours these animals were indistinguishable from normal rats. In the group which received 0·1 milligramme per hundred grammes the animals which survived had symptoms of only moderate severity, but in the first two groups in the table all the rats were severely affected.

Post Mortem Findings.

There was some œdema at the site of injection spreading on to the abdominal wall. The blood was fluid and there were no obvious clots in the heart or great vessels. The clotting time was normal (four, four, four and a half and four and a half minutes). In many the bladder was empty, but in four there was hæmoglobinuria of varying degree.

There were almost invariably petechial or massive hæmorrhages in the lungs. Petechial hæmorrhages in the thymus were common. The body tissues were frequently somewhat œdematous and there was free fluid in the thorax and peritoneum

in several animals. Excess of bile stained mucus in the small intestine was an almost constant finding.

EFFECTS IN THE MOUSE.

A preliminary series of injections was made by the tail vein in white mice; the results of these are set out in Table IX.

TABLE IX.
Results of Intravenous Injection in Mice.

Number of Animals.	Average Weight in Grammes.	Dose in Milligramme per 20 Grammes.	Result.
1	20	0·40	Death in 18 minutes.
2	27	0·30	Death in 23 and 76 minutes.
2	25	0·20	Death in 77 and 96 minutes.

In none of these animals were there any immediate symptoms and as the symptoms were almost purely neurotoxic and since no clear evidence of thrombosis was obtained, it was decided to use the intravenous route to determine the "characteristic" of the venom for this species. The results are set out in Table X, the venom being used in a concentration of 0·1 milligramme per cubic centimetre for the first group and 0·05 milligramme per cubic centimetre for the others.

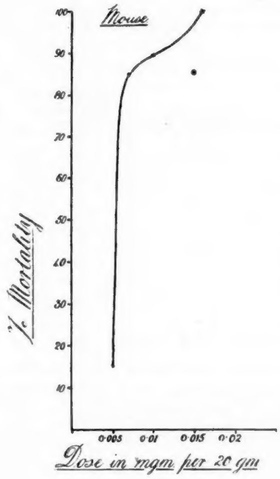
TABLE X.
Results of Intravenous Injection in Mice.

Number of Animals.	Average Weight in Grammes.	Dose in Milligramme per 20 Grammes.	Mortality. %	Time of Death.
12	25	0·016	100	Six died in 4 hours and the remainder within 15 hours.
19	21	0·01	89·5	Seven died in 4½ to 5 hours, five died in less than 12 hours, three in less than 18 hours, two on the second day, and two survived.
20	20	0·007	85	Five died in less than 12 hours, one in 15 hours, nine in less than 17 hours, one in 24 hours, and three survived.
20	20	0·005	15	One died in less than 17 hours, one in 18 hours, one on the second day, and seventeen survived.

Graph II is the "characteristic" of the venom for this species. The curve is very steep between 0·005 and 0·007 milligramme and the certainly lethal dose is probably not much greater than 0·01 milligramme per 20 grammes or 0·5 milligramme per kilogram.

Symptoms.

There is no preliminary collapse and the first symptom noted is loss of power in the hind limbs, the mice moving with dragging gait. This is followed, after an interval depending upon the dose, by a general "quiet" paralysis with distinct loss of tone, though in a few animals "starting" or convulsive movements can be observed from time to time. Hæmoglobinuria is not uncommon.



GRAPH II.
"Characteristic" for the venom of *Denisonia superba* in the mouse. The venom (except in the group with 100% mortality) was injected intravenously in a concentration of 0·05 milligramme per cubic centimetre.

Post Mortem Findings.

There is no obvious clotting in the heart or great vessels, though in one animal congestion of the bowel suggested that possibly a small thrombus might have been present in the portal vein. In forty-two autopsies thirty-eight mice had hæmorrhage of varying degree in the lungs and in the remainder these organs were congested. In most the small intestine contained excess of bile stained mucus. The spleen was not enlarged and except in the one case mentioned above the intestine was not congested. Thirteen mice had hæmoglobinuria of varying degree and as in many the bladder was empty, the incidence of this condition was probably much higher than these figures suggest.

The results of subcutaneous injection were obtained in a smaller number of animals, venom being used in a concentration of 0·05 milligramme per cubic centimetre and the injections being made in the flank. They are summarized in Table XI.

TABLE XI.
Results of Subcutaneous Injection in Mice.

Number of Animals.	Average Weight in Grammes.	Dose in Milligramme per 20 Grammes.	Result.
6	19	0·024	Three died in less than 12 hours, one in 13 hours, one in 14 hours, and one on the second day.
6	19	0·020	One died in 13 hours, two in 13¾ hours, and three survived.
6	20	0·016	One died in less than 12 hours, one in 13 hours, and four survived.
6	19	0·012	Two had slight paralytic symptoms, but all survived.

The certainly lethal dose by the subcutaneous route is therefore about 0·024 milligramme per 20 grammes or 1·2 milligramme per kilogram.

The symptoms and *post mortem* findings were so similar to those obtained following intravenous injection as not to warrant separate description. In all the animals except four in the last group which showed no symptoms, paralysis of the limbs and collapse were evident in twelve hours. In those which survived, recovery was complete by the end of the second day.

In Table XII the certainly lethal doses for the various species investigated are summarized and also the subcutaneous-intravenous index.

TABLE XII.

Certainly Lethal Dosage of Copper-head Venom in Laboratory Animals.

Species.	Certainly Lethal Dose. Intravenous in Milligramme per Kilogram.	Certainly Lethal Dose. Subcutaneous in Milligrammes per Kilogram.	Subcutaneous-intravenous Index.
Horse	—	about 0·02	—
Cat	—	about 1·2	—
Rabbit	0·3	0·7	2·66
Guinea-pig	0·015	0·06	2·5
Rat	about 0·9	1·4	1·56
Mouse	about 0·5	1·2	2·4

Fairley found that the certainly lethal dose for sheep by the intravenous route was 0·15 and by the subcutaneous route 0·1 milligramme per kilogram, the subcutaneous-intravenous index being 0·7 approximately. For the animals which I have investigated, the index is about 2·5 and the figure obtained for the rat (1·56) may be too low, since the estimated certainly lethal dose by the intravenous route is based on too small a number of observations. The evidence presented here, like that obtained by Fairley in experiments with sheep, points to the absence of thrombase from this venom. This being the case, since variation in tendency to clotting in different species is excluded as a cause of variation in the subcutaneous-intravenous index, it might be anticipated that the index would be about the same in all the species examined. This, however, is not the case and departures from the most usual value may be explained either by varying rates of elimination of the venom by the kidney, bowel and other channels, by varying rates of destruction of the venom in different species or by varying rates of absorption of neurotoxin. This question will form the subject of further investigation.

With all the venoms studied there seems to be increased activity of the secreting glands. The wet mouth so often observed may result from paralysis of the swallowing mechanism, though I am inclined to believe that increased salivary secretion occurs. There is certainly in nearly all species an increased flow of bile and diarrhœa is by no means uncommon. Increased secretion of tears has also been noted, though this may have been due to the irritation of the conjunctiva by foreign bodies. Sweating was common in horses injected with tiger snake venom.

While the increased flow of bile may, as Fairley has suggested, be related to the stimulus of increased blood destruction, it seems not improbable that it is part of a natural mechanism for removing venom from the body. The clinical picture in many animals injected with doses in the neighbourhood of the certainly lethal dose (not causing overwhelming symptoms and rapid death) strongly suggests that there may be several avenues for the removal of poison from the body and that snake venoms have a definitely stimulant action on the secretory glands. This venom and that of the death adder in which thrombase is absent, are particularly suitable for the investigation of these various possibilities, which will form the subject of later studies. The evidence presented in the present paper for the presence of an "anticoagulin" in the venom of the Australian copper-head is not nearly so convincing as that afforded by Fairley's experiments in sheep, but on the whole supports the view that the venom has an anticoagulant action.

Finally, the observations recorded here indicate that the venom of the Australian copper-head (*Denisonia superba*) is less potent than that of the tiger snake (*Notechis scutatus*) and of the death adder (*Ancanthophis antarcticus*), but more so than that of the black snake (*Pseudechis porphyriacus*). Different species exhibit wide variations in susceptibility to the venom, the guinea-pig and sheep being most sensitive and the cat, rat and mouse being less susceptible. There is no suggestion that, as in the case of the venom of the tiger snake, the certainly lethal dose for man is likely to be of the same order as that of an animal of similar body weight, like the sheep. With this venom species susceptibility far outweighs any difference dependent upon the average body weight of the species in question. It is probable that the lethal dose for man lies between 0·02 and 1·4 milligrammes per kilogram.

These limits are extremely wide and a closer approximation to the certainly lethal dose for man might be afforded by the investigation of further species. For the monkey the certainly lethal dose is evidently not far removed from 0·2 milligramme per kilogram.

A male monkey (*Macacus rheusus*), weighing 1·87 kilograms, was injected subcutaneously with this venom in a dose of 0·2 milligramme per kilogram. He became drowsy in about six hours and within seven hours exhibited general muscular weakness. Five hours later this had become more pronounced and all the movements were ataxic. By the twenty-second hour paralysis was complete, except for the diaphragm and facial musculature, the angle of the mouth being retracted and the eyebrows elevated with each respiration. The thorax was immobile, respiration being wholly diaphragmatic; the limbs were toneless and the animal lay in any position in which placed. The paralysis was typically "quiet" and "starting movements" were absent. The action of the heart was good, but there was evident vasomotor failure by the forty-eighth hour, when the animal was moribund. At this time the body temperature was 31° C. and the respiration rate 22 per minute and still quite regular. The animal remained paralysed and died on the seventh day after the injection.

It is probable that the lethal dose for man lies nearer to the values for the guinea-pig, sheep, horse and monkey than to those of the cat, rat and mouse.

The neurotoxic action of this venom is rapid and judged by the associated profound loss of tone, is mainly on the lower motor neurones. The lack of tone in animals injected with this venom is much more striking than is the case with tiger snake or death adder venom and possibly as a result of more rapid absorption related to the absence of thrombase, paralysis is also more rapid in onset in the case of subcutaneous injections of this venom than when tiger snake venom is injected. Other factors, such as the rate of absorption in nervous tissue, may be the cause of this difference in action.

Whereas with the venom of *Notechis scutatus* the phrenic nerves or their end plates in the diaphragm may in some species (the guinea-pig) be sometimes affected, with this venom this phenomenon was noted only in one or two cases. The usual result was depression of the sensitiveness to stimuli of the sciatic nerves as well as of the phrenics, though often the diaphragm responded well to stimulation of the phrenics immediately after death when the heart was still beating. The site of action of this and other Australian venoms on the nervous system and on the respiratory apparatus requires further analysis.

CONCLUSIONS.

1. The venom of the Australian copper-head contains neurotoxin, hæmorrhagin and hæmolysin, the first being mainly responsible for its lethal effects. Thrombase is absent.
2. No indication is afforded by these experiments of the certainly lethal dose for man, save that it probably lies between 1·4 and 0·02 milligramme per kilogram.
3. The subcutaneous-intravenous index in three of the four species investigated is about 2·5.
4. It is suggested that the Australian snake venoms have a general stimulant action on bodily secretion and that this may furnish an important means for the elimination of poison.

Obituary.

FRANCIS WASHINGTON EVERARD HARE.

DR. E. SANDFORD JACKSON has kindly written the following note in appreciation of the intellectual achievements of Francis Washington Everard Hare.

News has reached Australia of the death of Dr. Francis Washington Everard Hare, once Assistant Resident Surgeon to the Brisbane General Hospital and later Medical Superintendent of the Charters Towers Hospital.

For some years after qualifying Francis Hare served in eastern waters in the Peninsula and Oriental Company's ships, after which he entered the service of the Brisbane General Hospital, in August, 1885. That was a year of much importance to the institution, by reason of the fact that in it, beside Dr. Hare, Miss Mary E. Weedon, now retired and living at Stanthorpe, and Mr. A. P. Payne of Sherwood, joined the staff. The former, under the title of Head Nurse, became head of its nursing staff, while the latter presided over the secretarial office. Dr. D. F. Brown, still happily connected with the dispensing staff of the hospital, had preceded all three, having been appointed in the early part of the year. All of these officers played their important part in the improved organization of the hospital methods which followed 1885. Thus they were concerned in many ways in good results under Hare's direction of his especial work.

Francis Hare immediately took over the medical charge of the fever wards. At that time it is not exaggerating to say that the lovely city of Brisbane had become a hot bed of what was then best known as typhoid fever (enteric). Hundreds of patients were admitted every year and among the individuals so affected there was a preponderance of immigrants. Migration from the Old Country to Queensland was not then the tiny stream that it is today. A fortnightly British India steamship brought not less than four hundred in every fortnight.

There was then no training school for nurses in the colony. There were no nurses experienced in fever nursing and indeed the medical staff of the hospital, including its superintendent or its honorary staff, had not had such opportunities of studying that branch of their work, as it pleased providence to give them in the ten years following the beginning of the year 1883.

The fever wards of the hospital with their annexes had been built before the year 1881 to accommodate about sixty patients with different kinds of infectious fevers. From 1882 onwards for some years all the beds with which they had been originally equipped, were filled with typhoid patients and half as many again had to be added as required to meet exigencies. Luckily the construction of the wards, due to the foresight of the late John Thomson (who had been in charge of the hospital at the time they were built), permitted this without running patients into any serious risk arising from a vitiated atmosphere. They were and are extraordinarily lofty, well provided with windows and with overhead ventilation.

From the advent of Miss Weedon in October, 1885, better things had been possible as regards the training of nurses, until in the latter half of 1886 it became possible to start the Brisbane Hospital School for Nurses. It is worthy of note that the period of training demanded from candidates for certification was at first only eighteen months and that among the first batches of trainees there was a large proportion who have since made their worthy mark all over Australia and in many parts of the world beside. Moreover, nurses of that date still hold their own in the best company.

In spite of improvements in nursing, which took place during the latter end of 1885 and in 1886, the mortality in the fever wards of the Brisbane Hospital remained unsatisfactory.

Francis Hare was an interested worker. He studied his cases carefully. He studied carefully, also, the scanty literature which was then available in relation to fevers. Murchison's "Fevers" was then a classic. There he read of a cold bath treatment of typhoid, introduced by a Dr. Brand in Switzerland. This seemed to him to promise a hope of reducing the mortality of the cases under his care to less alarming proportions. Towards the end of 1886 plans were laid to introduce the treatment by cold bath on the lines laid down by Dr. Brand and to accomplish this somewhat suddenly. A beginning was therefore made on the first day of January, 1887.

In this way it was obvious that a more accurate comparison with the work of former years could be made. It was thought, too, that thus might more easily be demonstrated the fact that no one could justly claim that any good result which might accrue, had been due to some other coincident change in methods. Indeed, no other change either in methods of diagnosis or in treatment was made. At the end of the year the mortality under the head of typhoid fever presented the figure 11·3 and in 1888 it was still further reduced to 6·8, approximately half the former average. Hyperpyrexia now belonged almost to the past, while the causes of deaths in typhoid were limited to those from hæmorrhage and perforation. Moreover, there had been no increase in the proportion of deaths from these two complications. This reduction in mortality represented, of course, a very important saving of valuable lives. A saving of from six to eight lives in every hundred is of great importance in a year when 595 patients are treated.

This saving of lives was due to the intense interest in the welfare of patients and to the extraordinary intellectual power of their chief medical attendant. It is not to be forgotten, of course, that his work was made much easier for him by Miss Weedon and the chief nurse in the fever wards, Miss Crosse, now of Walcha, and all their assistants. But how could they help under such a master acquiring an interest in and a knowledge of fever nursing which was more than ordinary? Many of them, too, carried that interest and knowledge of their work to the other ends of Australia and indeed of the world, to the great advantage of their fever patients. Such then was the widespread effect of Francis Hare's work. Not only so, but his immediate medical colleagues were the better for his

example. There were no differences of medical opinion internal to the hospital staff, honorary or resident.

The publication of his book on cold bath in typhoid fever, which took place after he went to Charters Towers, made it possible for medical men all over the world to learn of his good work. That book, though more than twenty-five years old, must still be a classic. It is a lesson in the careful handling of statistics.

Were the people among whom he worked appreciative of his magnificent results? On the whole—yes! There were, however, one or two eccentric members of the noble profession who waxed very wrath at the unheard of idea of "plunging a patient in a high fever into cold water." Thus it was that one wrote of Hare's treatment in a pamphlet entitled "Shall They Die?" this little brochure being, as is usual in such cases, published in a yellow back. It is true that, little thing as it was, it created a good deal of prejudice against the bath in the minds of a few patients; but this was easily enough overcome and the good work went on with little interruption. Above all, for many years after Hare's departure to another hospital the improvement in mortality was maintained. For ten years from 1887 to 1896 inclusive the average in 1902 cases was only 7·5% under the cold bath treatment.

Francis Hare retired from the hospital in 1889 to take charge of the Charters Towers Hospital. There he remained for about ten years to the great advantage of that institution. After leaving the Towers he came to Brisbane and began private practice. He was subsequently appointed Inspector of Hospitals and there is at least one important report from his hands upon the hospitals of this State buried among other papers in the pigeonholes of a Government office. It would probably do no harm if it were aired.

Later he retired from the position of Inspector of Hospitals and again went into practice in Brisbane, holding at the same time the position of Medical Officer to the Diamantina Hospital for Chronic Diseases. About this time he paid much attention to the question of dietetics and was engaged in the preparation of a book on that subject.

He married Miss Ethel Bell, daughter of the late G. T. Bell, and soon after left Queensland for London. There he became superintendent of an institution for the relief of inebriates at Norwood and found time to publish his book on dietetics, under the title of "The Food Factor in Health and Disease," as well as more than one other on the treatment of inebriates.

Shortly after the war Francis Hare's health caused his friends considerable anxiety. A hemiplegia, described as very slight was the result. Doubtless it was a second attack of the same complaint which carried from us at the age of seventy-three one of the most intellectual and successful physicians the State of Queensland has ever known.

Francis Hare leaves in England his widow and one son to mourn their loss.

Correspondence.

VARICOSE ULCER OF THE LEG.

SIR: Dr. A. W. Shugg has written enthusiastically of the proper use of Unna's paste in varicose ulcer in the journal of January 26. The same subject has been fully dealt with by Fay Maclure in the same journal recently and by W. Ure Smith in *The British Medical Journal* of January 27, 1928, page 137. Fay Maclure alone offers an explanation of the principle of the treatment adopted, but his reasoning, in my opinion, begs the question.

The limiting membrane of every cell, of every organism, is there to quell pump action. Rapid healing of surface wounds is called for and the promotion of scab-formation is indicated. I have continually asked for the rationale of methods empirically adopted from time to time, as in the present case, in the application of bismuth-iodoform-paraffin paste in other conditions and in modern methods of the treatment of burns and scalds.

No explanation has been forthcoming. Yet there is one principle underlying them all. Healing, with a minimum of exudation, can only proceed in the absence of irritation, physical, chemical or biological; in other words, friction, continued use of antiseptics or infection. In the case under review, friction is eliminated by the paste and bandages, chemical irritation is mitigated by the use of one of the least irritating antiseptics, infecton is inhibited to some extent by this reagent, but the exudation which it is admitted is present necessitating a change of dressing, is the result of mild continued chemical action and infection incompletely subdued. In plain terms, we have in all cases the unconscious imitation of Lister's antiseptic method but an imperfect one. As the originator of the paste method, I suspect that Professor Unna devised his method on Listerian lines without a proper understanding of them. Unna was fifteen years old when the antiseptic method was introduced; his practice, therefore, must have been influenced by Lister's teaching.

The comparatively wide adoption of Unna's method—it has even been successfully exploited by a quack in this city for some years—has not prevented the distribution among all readers of *The British Medical Journal* of a *questionnaire* on varicose ulcer. Evidently none of the prevailing methods is regarded as satisfactory.

It does not appear to be of any uses to ask the official representatives of modern wound treatment to try the antiseptic method, but this pelican crying in the wilderness may be heard by some thoughtful and unbiassed mind who will think it worth while to repay some of the debt he owes the greatest mind that ever thought for his fellow men in anguish. To him I say: "Try this: disinfect the ulcer with a solution of forty grains of chloride of zinc in one ounce of water! Apply a copious dressing of double cyanide gauze; cover this with lint soaked in one in forty carbolic oil! Change the dressing next day without exposing the wound! Cleanse the skin around the ulcer with swabs wet with 5% carbolic lotion. Change the dressing less frequently, not allowing any exudation to penetrate the materials until it is found that it has firmly adhered to the wound! Cut away the loose parts, apply a little plain gauze soaked in alcohol and keep in place with a light bandage! From now on instruct the patient to drench the dressing without undoing it with methylated spirit twice a day! Warn the patient that spirit is inflammable! The artificial scab will detach itself in two or three weeks. If at any time moist exudate has come to the surface of the dressing or the skin, begin *da capo*."

Yours, etc.,

A. C. F. HALFORD.

Brisbane, January 26, 1929.

Postscript.—Dougle cyanide gauze as made today contains uncombined cyanide and is therefore irritating. I always rinse it well in carbolic lotion, one part in forty, before applying it to a wound. If the gauze were made strictly according to Lister's directions (see "The Extra Pharmacopœia" nineteenth edition, page 461), this treatment would not be necessary as the gauze is entirely bland and unirritating. I think it likely that this unfortunate feature of the gauze of today is due to the futile and ridiculous practice of sterilizing it by superheated steam after manufacture. Of course, we must go one better than Lister.

OBSTETRICAL PRACTICE.

SIR: In your issue of January 26, 1929, Mr. Hugh Cairns comments on the report of a discussion on a case of suboccipital dermoid cyst by the Melbourne Pædiatric Society.

I should like to point out that the meeting, the report of which appeared in the issue of October 6, 1928, was held on May 9, 1928, six months previously and that no copy of my remarks was submitted to me for correction prior to publication.

I am reported to have stated that the average survival period after operation was six months. Actually I said that six months was the average survival period in children

for the most malignant variety, namely the medulloblastomas and that other types showed a much more favourable prognosis.

As Mr. Cairns correctly surmises, the article referred to by me was "The Intracranial Tumours of Preadolescence," by Harvey Cushing. This, together with my personal experience of witnessing Cushing's work and results at the Peter Bent Brigham Hospital, Boston, in 1925, was quoted in order to stimulate members to the recognition of the fact that cases of subtentorial tumours in children were not uncommon and that, contrary to the belief of many, in a large percentage of cases the result of surgical interference was excellent.

It was urged, however, that early diagnosis should be the aim, in order that surgical treatment may be instituted before hydrocephalus had advanced to the stage when vision would be permanently damaged. I am obliged to Mr. Cairns for drawing attention to this report, which was a very condensed and decidedly inaccurate representation of the views expressed at the meeting.

Yours, etc.,

CHARLES H. OSBORN, F.R.C.S., F.C.S.A.

32, Collins Street, Melbourne.
February 3, 1929.

SIR: In his interesting if perhaps somewhat startling paper Dr. Kesteven once again raises the question of the standardization of obstetrical treatment.

Referring to this question, it may not be out of place to recall the very striking statement of that master of obstetrics, Professor Munro Kerr, in his classic work on "Operative Midwifery": "The obstetrician must ever avoid taking up an extreme position and becoming a partisan for or against any particular treatment. Progress in obstetrics has been much retarded in all ages by those who have unfortunately adopted such an attitude. When one finds equally distinguished obstetricians holding absolutely different views, it is almost certain that the right is with none.

"No hard and fast rules can be laid down and different obstetricians of equal ability, knowledge and experience may act differently under the same circumstances."

Yours, etc.,

"READER."

Melbourne.
February 7. 1929.

SIR: Dr. Kesteven's reply to my letter does not disprove the fact that his procedure in 24% of his cases is none else than *accouchement forcé*, but I am gratified to learn that my idea of discourtesy was incorrect and that merely frank comment was implied.

If Dr. Kesteven would attend a monthly meeting of the obstetric staff of the Women's Hospital, he would perhaps be convinced that the members were not uncritical, but rather the opposite and it is now necessary for me to point out to him that the higher morbidity rate for forceps deliveries also applies to those cases who have attended the ante-natal department and who have neither been complicated nor maltreated in any way.

Dr. Kesteven is correct regarding my part in the research into the vaginal flora, but I do not express my emphatic opinion on such. I am merely content to quote, for instance, Professor B. P. Watson, of Columbia University, New York, from an article on *post partum* pelvic infections read by him at the last annual meeting of the American Gynecological Society. He states: "There can be no doubt, therefore, that streptococci do occur in the vaginas of apparently healthy women" (*American Journal of Obstetrics and Gynecology*, October, 1928). It was the last idea in my mind that my signature should be in bad taste, but my zeal for the welfare of obstetric science and my concern as an obstetric teacher at the persistent maternal morbidity and mortality rates led me to express the experience and qualifications on which my criticism was based.

Yours, etc.,

HUBERT JACOBS.

Collins Street, Melbourne.
February 15, 1929.

POST-GRADUATE STUDIES.

SIR: All will agree with "Country Practitioner" in his plea in your issue of January 26, 1929, for facilities for post-graduate study in Australia. He is, however, in error in suggesting that city and suburban practitioners are at present more favourably placed in this respect than are country practitioners. For the last two years the Public Medical Officers' Association of New South Wales has striven to secure the establishment of regular post-graduate teaching in Sydney, but so far without success. Might I suggest that "Country Practitioner" and his colleagues interest the local medical associations in this important matter? The weight of public opinion within the profession may be able to effect more than has the earnest advocacy of individuals.

Yours, etc.,

H. HASTINGS WILLIS.

Sydney.
February 1, 1929.

DIET IN HYPERCHLORHYDRIA.

SIR: If you consider it a suitable subject, would you kindly have an article written for the journal on "diet in hyperchlorhydria"? Otherwise a request inserted in "Correspondence" for advice by those who have had to conform to its stringency. I have read the available diet books and articles *et cetera* and though there is some general agreement, others put forward quite different and almost opposite articles of food to be taken and it makes one wonder if an academic or "arm-chair" attitude has not crept in unwelcomed.

Lately having been personally put on such diet with relief to a certain extent, I would be grateful for assistance by those who have had the trouble and distress already in a severe form (a slight attack would not give the required information) if you would kindly forward their opinion and advice to me.

Yours, etc.,

"HYPERCHLORHYDRIA."

January 30, 1929.

OPERATION FOR FRONTAL SINUSITIS AND DACROCYSTITIS.

SIR: In your last issue, under heading of extracts, mention is made of a new method of operating upon frontal sinus. This is the procedure I adopted thirty years ago and still use today, excepting that I follow Dr. Goodsell's suggestion of packing the sinus until it is occluded by granulation tissue, as occasionally I found atresia of the infundibulum. This week I have seen two patients who were operated upon twenty-five and twenty years ago respectively with excellent æsthetic *et cetera* results.

A new operation is also described for dacrocystitis. This I have performed for twenty years with uniformly satisfactory results. The technique differs from mine in one respect only. I excise the anterior wall of the sac. The resulting scar is practically invisible and the operation is very easy to perform. Care must be taken to remove a good area of bone or the suturing of the nasal mucosa to that of the sac will be tedious.

Yours, etc.,

W. KENT HUGHES.

Melbourne.
February 8, 1929.

A WARNING.

SIR: The warning appearing in the correspondence in your February 2 issue above the signature Merrick O'Reilly was well given. The young man is a magsman and morphomaniac.

I would like to add the information that on December 13 last a young man answering the description given was brought to my surgery by car under the name Walker, with symptoms of renal colic. He simulated these very well and with the tale that, having been given a "lift" by the man known to me, he had suddenly developed the symptoms in the car. He remained in bed at the local hotel and had me out in the night for more morphia.

He was easier next day, disappeared from the hotel and (to his sorrow) accidentally hailed me for a "lift" on a country road.

A few hours after information to the police helped to locate the "gentleman" and it was ascertained that he had bluffed other medicoes, hospital authorities and boarding house keepers in this State under the name of Blair.

His tales have been full of detail of X ray, ureteric and other examinations by leading men in the capital cities, but I understand he is serving time now.

Medical men will be well warned to keep a lookout for him in the next few months.

Yours, etc.,

ROBT. M. W. WEBSTER.

Campbell Town,
Tasmania.
February 7, 1927.

FACILITIES FOR POST-GRADUATE STUDY OF PÆDIATRICS.

SIR: A steadily increasing interest and demand for post-graduate refresher courses in medicine, surgery, obstetrics and pædiatrics by both city and country practitioners is a healthy fact which, I understand, the British Medical Association is soon to take special steps to meet. Several queries have been made in these columns as to the present opportunities for such work here and abroad.

As regards pædiatrics, probably the most recent, widest and most difficult of the specialties, the facilities today are not yet fully organized, even in Europe and a brief list of some of the most important centres there may be of value to a post-graduate anxious to pursue this fascinating branch and to concentrate his time abroad into as short a space as possible.

Taking London first, the Fellowship of Medicine, 1, Wimpole Street, W.1, usually know for some months ahead just when short special courses of two or three weeks' duration will be held in the various children's hospitals. The Queen's Hospital for Children, The Infants' Hospital, Westminster, and the Shadwell Children Hospital and latterly The Hospital for Sick Children, Great Ormond Street, all hold biannual full-time courses limited usually to about twenty members and closely covering a wide range of work. Fees vary from three guineas to five guineas. The Great Ormond Street course is specially to be recommended as the whole services of the hospital are for the time being concentrated on post-graduate teaching and the staff themselves have already had a special training in this class of work. Clinical assistantships (unpaid) and requiring the devotion of one or two whole mornings a week at the out-patient department of the hospital are fairly easily obtainable, providing men are prepared to remain for the full six months' appointment. One remains with the same out-patient physician all this time and sees an extraordinarily large series of selected cases in this time. The position also considerably strengthens a later application for a house post.

Dr. Eric Pritchard at the Infants' Hospital holds biweekly round table conferences, as he calls them, on any problem of infant feeding which may be presented during the afternoon. Naturally enough, he does most of the talking and his wide and long experience makes these gatherings most valuable. Dr. H. C. Cameron, in charge of the Childrens' Department of Guy's Hospital, on two mornings per week settles in his characteristic common-sense fashion many of the psychological problems of the nursery. What one may term laboratory pædiatrics, is best seen at the children's research department at St. Thomas's Hospital.

G. F. Still has charge of the children's ward at King's College and it is worth the two hours' journey there and back to watch this famous pioneer at work. Dr. Reginald Miller conducts the best-run rheumatic clinic in England at Paddington Green and is particularly kind to interested visitors. The wards, museum and special departments of Great Ormond Street are at the disposal of the post-graduate for a small monthly fee either for a personal examination of the cases or together with the physician in charge. The convalescent home and heart home associated with this hospital are usually inspected during one of their organized courses of instruction.

Leaving London, Birmingham (Dr. Leonard Parsons) with their well-known rheumatic home at Baskeville, Liverpool (Dr. Dingwall Fordyce), Newcastle (Dr. Spence) and Manchester (Dr. Ashby and Dr. Lapage) are probably the best provincial centres to see. In Scotland from a medical point of view Glasgow is deservedly well known owing to the personality and enthusiasm of Professor Leonard Findlay who is the sole director of teaching, research and therapy. He has under his care some three hundred children and his thorough methods for teaching, observation and after-care will well repay a prolonged visit and give one a lasting impression of the splendid practical results which can be obtained by coordination of research and the unification of medical control.

On the Continent, Vienna, Berlin and Zurich are well known for this specialty. von Pirquet at the former and Emil Feer at the latter are readily approachable, helpful and informative. A letter addressed personally to either of these men, preferably in German, a knowledge of which is a tremendous aid, will elicit a welcoming reply.

I have not had personal experience of America, but from conversation with American pædiatricians in Europe I should think that there is little there which London cannot eclipse. One exception should be made; W. McKim Marriott directs a large research hospital at St. Louis, where he has done excellent original work on many aspects of infant feeding and diarrhœa. I shall be glad to send a prospectus of his somewhat expensive biannual post-graduate session to any one interested. It is now becoming possible for exchanges to be made between members of the resident staffs of certain children's hospitals in America and London for periods of approximately six months each.

In Sydney it is to be hoped that the favourable comment following the post-graduate course held at the Royal Alexandra Hospital for Children over a year ago will encourage the board to hold such another very soon. After all, as regards equipment and accommodation, Europe can scarcely show an equal to this splendid, up-to-date institution.

Yours, etc.,

KEMPSON MADDOX, M.B., M.R.C.P.

141, Macquarie Street, Sydney.
(Undated.)

CANCER IN MICE.

SIR: In your editorial of this date dealing with my results you have made two slips on page 250.

(i) The forty-five boiled milk inoculated mice are stated to have yielded "but six" epithelial tumours, whereas in my article (page 161, second column, Group C) the incidence is correctly given as "carcinoma 13, adenoma and papilloma 6," a total of nineteen.

(ii) You then run on, "None of the control mice had any tumours other than mesoblastic," whereas at the same place I state the incidence of both Group B and Group D as "carcinoma 2, adenoma 1."

My tabulated statement on page 181, column 2 is clearly stated to refer to mesoblastic tumours after removal of all those which are frankly enlarged glands.

I am glad you advise caution in accepting alleged facts in regard to cancer in mice. They seem to be very tricky animals, as indeed appears from the incident related by Herodatus. A statue with a golden mouse in his hand had been set up by the Egyptians to commemorate the destruction of Sennacherib's 185,000 men (pneumonic plague?) and it bore the inscription, "Whoso looketh upon me let him not be too cocksure of himself."

Yours, etc.,

THOMAS CHERRY.

The University, Melbourne,
February 23, 1929.

[We regret that we made the error to which Dr. Cherry refers. Unfortunately he has not described the epithelial tumours grouped in such a manner that those encountered in mice fed on boiled milk and inoculated are contrasted with those encountered in mice fed on boiled milk but not inoculated. It is true that the figures are given in the tabulated records. The argument used, however, is not affected by the error. The frequency among the inoculated was nineteen and among the uninoculated three. These figures are too small to permit deductions without confirmation in other series of experiments.—ED.]

Congress Notes.

THE AUSTRALASIAN MEDICAL CONGRESS.

THE executive committee of the third session of the Australasian Medical Congress (British Medical Association) has made considerable progress in its work of organizing the session. It is anticipated that the scientific value of the contributions and discussions will be of a high order and that ample time will be allowed for the debates. As the science and art of medicine and its many branches advance, the didactic value of papers read at congresses is increased each year.

Provisional Programme.

The following is a provisional skeleton of the programme.

Monday, September 2, 1929.

9.30 a.m.—Registration of members.
Afternoon.—Garden party and reception.
Evening.—Inaugural meeting and address by the President.

Tuesday, September 3, 1929.

9.30 a.m.—Full meeting of Congress; subject: "What is Being Done in Australia towards Cancer Research?"
2 p.m.—Meetings of the sections; chairmen's addresses.

Wednesday, September 4, 1929.

9.30 a.m.—Meetings of the sections.
11 a.m.—Combined meetings:
Sections of Radiology and Medical Electricity and of Dermatology: "The Treatment of New Growths of the Superficial Parts."
Sections of Surgery and of Orthopædics: "Compound Fractures of the Lower Limb."
Sections of Medicine, of Pathology and Bacteriology and of Preventive Medicine and Tropical Medicine: "Prevention, Diagnosis, Treatment and Control of Scarlet Fever and Diphtheria."
Sections of Neurology and Psychiatry and of Ophthalmology: "The Value of Ocular Science in Neurological Diagnosis."
2 p.m.—Meetings of the sections.
Section of Naval, Military and Air Medicine and Surgery: "Gas in Warfare, Particularly as Regards Civil Population."

Thursday, September 5, 1929.

9.30 a.m.—Meetings of the sections.
11 a.m.—Combined meetings:
Sections of Medicine, Neurology and Psychiatry, of Surgery and of Orthopædics: "Trauma in Relation to Functional Disorders."
Sections of Preventive Medicine and Tropical Medicine and of Naval, Military and Air Medicine and Surgery: "Aviation From Its Medical Aspect."
Sections of Obstetrics and Gynæcology and of Pathology and Bacteriology: "Endometriomata."
2 p.m.—Combined meetings:
Sections of Pædiatrics, of Orthopædics and of Radiology and Medical Electricity: "Bone Dystrophies."
Section of Obstetrics and Gynæcology: Discussion on Maternal Morbidity.

Friday, September 6, 1929.

9.30 a.m.—Combined meetings:
Sections of Medicine, of Oto-Rhino-Laryngology, of Pædiatrics and of Radiology and Medical Electricity: "Chronic Pulmonary Infections in Relation to the Upper Respiratory Tract."
11 a.m.—Sections of Surgery, of Pathology and Bacteriology and of Radiology and Medical Electricity: "Bone Sarcoma."
Sections of Pædiatrics, of Obstetrics and Gynæcology and of Preventive Medicine and Tropical Medicine: "Natal and Neo-natal Mortality and Morbidity."
2 p.m.—Meetings of the sections.
Section of Medical Literature and History: "Development and Progress of the Medical Profession in Australasia."

President of Congress.

Owing to unforeseen circumstances Sir Alexander MacCormick has been compelled to resign his position as President of Congress. The Council of the New South Wales Branch has nominated Dr. G. H. Abbott for the position. The appointment will be made by the Federal Committee of the British Medical Association in Australia at its meeting on April 10 and 11, 1929.

AN INGENIOUS TEAPOT.

IT is the nature of human beings to acquire a taste for certain poisons that can be tolerated in relatively large doses without immediate lethal results. Tobacco, alcohol, tea and coffee may be instanced as the commonest of the poisons that are used habitually. A sensible person will endeavour to obtain the pleasing flavour of his chosen beverage and at the same time to reduce the harmful effects to a minimum. When tea has been brewed for a prolonged period the infusion is found to contain bitter extractives that cover the fine flavour of the leaves. In order that tea may be brewed under proper conditions, the Robur Tea Company, Limited, has devised a teapot that is both ingenious and purposeful. It is made of hard white metal heavily plated with sterling silver. The leaves are placed in a loose percolator of special shape. Water at boiling point, that is when the ebulition is brisk, is poured into the scalded pot. The percolator carrying the necessary amount of tea leaves is inserted and allowed to stand for five or at most six minutes. The percolator is twisted a few times and then removed. The infusion can be kept hot and enjoyed without getting bitter or taking up harmful astringent substances. The teapot is worthy of the consideration of those who desire to have a pleasant and harmless drink. The manufacturers are bringing this excellent invention to the notice of the medical profession and are offering one to each practitioner at a very low price. We can recommend this device.

MEMORIAL TO THE LATE HARRY JOHN CLAYTON.

THE following additional subscriptions have been received by the Honorary Treasurers of the Harry John Clayton Memorial Fund:

	£	s.	d.
Previously acknowledged	272	7	9
Mrs. J. H. Clayton	100	0	0
T. Buckland	10	10	0

	£	s.	d.
J. L. Hudson and Mrs. Hudson	10	1	0
Miss L. M. Clayton	10	0	0
Mrs. T. V. Nicholls	10	0	0
Drs. N. M. Gibson and C. J. Wiley	5	5	0
Dr. Herbert Schlink	5	5	0
J. W. Ferguson (Miss McClintock Ferguson)	5	0	0
Eric S. Kelynack	3	3	0
Miss L. Alford	2	2	0
Dr. Burke-Gaffney	2	2	0
Dr. Cotter Harvey	2	2	0
Dr. J. W. Hoets	2	2	0
Dr. James Hughes	2	2	0
Dr. J. A. James	2	2	0
Walter W. Lyon and A. R. Lempriere	2	2	0
Dr. J. R. Maude	2	2	0
Dr. Harry C. Moxham	2	2	0
L. W. Seaborn	2	2	0
N. W. Strahorn	2	2	0
Dr. T. Nickson	1	1	6
J. P. Abbott	1	1	0
J. Val Boyle	1	1	0
Dr. A. M. Edwards	1	1	0
Dr. N. M. Gregg	1	1	0
Kay Goward	1	1	0
Miss F. Hattersley and Miss S. F. Hattersley	1	1	0
Dr. H. W. Kendall	1	1	0
A. Pratt	1	1	0
Dr. W. B. Clipsham	0	10	6
Total to date	£464	13	9

Books Received.

A COMPEND OF DISEASES OF THE SKIN, by Jay Frank Schamberg, A.B., M.D.; Eighth Edition, Revised and Enlarged; 1929. Philadelphia: P. Blakiston's Son and Company. Crown 8vo., pp. 340, with illustrations. Price: $2.00 net.

EPIDEMIC ENCEPHALITIS IN ASSOCIATION WITH PREGNANCY, LABOUR AND THE PUERPERIUM, by Frederick Roques, M.A., M.D., M.Chir. (Cantab.), F.R.C.S. (England); 1928. Manchester: Sherratt and Hughes. Royal 8vo., pp. 150. Price: 15s. net.

SEX AND THE YOUNG, by Marie Carmichael Stopes; 1929. London: G. P. Putnam's Sons. Demy 8vo., pp. 190. Price: 3s. 6d. net.

Diary for the Month.

MAR. 19.—New South Wales Branch, B.M.A.: Council.
MAR. 20.—Western Australian Branch, B.M.A.: Branch.
MAR. 21.—New South Wales Branch, B.M.A.: Branch.
MAR. 22.—Queensland Branch, B.M.A.: Council.
MAR. 26.—New South Wales Branch, B.M.A.: Council.
MAR. 27.—Victorian Branch, B.M.A.: Council.
MAR. 28.—South Australian Branch, B.M.A.: Branch.

Medical Appointments Vacant, etc.

FOR announcements of medical appointments vacant, assistants, *locum tenentes* sought, etc., see "Advertiser," page xx, xxi.

ALFRED HOSPITAL: Medical Appointments.

AUSTIN HOSPITAL FOR CHRONIC DISEASES, HEIDELBERG, VICTORIA: Junior Resident Medical Officer.

BENEVOLENT SOCIETY OF NEW SOUTH WALES: Resident Medical Officer.

CHARTERS TOWERS DISTRICT HOSPITAL, QUEENSLAND: Resident Medical Officer.

HAMILTON AND DISTRICT HOSPITAL, VICTORIA: Resident Medical Officer.

NEW SOUTH WALES BRANCH OF THE BRITISH MEDICAL ASSOCIATION: Medical Secretary.

PERTH HOSPITAL, WESTERN AUSTRALIA: Pathologist.

ROYAL PRINCE ALFRED HOSPITAL, NEW SOUTH WALES: Honorary Vacancies.

Medical Appointments: Important Notice.

MEDICAL practitioners are requested not to apply for any appointment referred to in the following table, without having first communicated with the Honorary Secretary of the Branch named in the first column, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

BRANCH.	APPOINTMENTS.
NEW SOUTH WALES: Honorary Secretary, 30 - 34, Elizabeth Street, Sydney.	Australian Natives' Association. Ashfield and District United Friendly Societies' Dispensary. Balmain United Friendly Societies' Dispensary. Friendly Society Lodges at Casino. Leichhardt and Petersham United Friendly Societies' Dispensary. Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney. North Sydney Friendly Societies' Dispensary Limited. People's Prudential Assurance Company, Limited. Phœnix Mutual Provident Society.
VICTORIAN: Honorary Secretary, Medical Society Hall, East Melbourne.	All Institutes or Medical Dispensaries. Australian Prudential Association Proprietary, Limited. Mutual National Provident Club. National Provident Association. Hospital or other appointments outside Victoria.
QUEENSLAND: Honorary Secretary, B.M.A. Building, Adelaide Street, Brisbane.	Members accepting appointments as medical officers of country hospitals in Queensland are advised to submit a copy of their agreement to the Council before signing. Brisbane United Friendly Society Institute. Stannary Hills Hospital.
SOUTH AUSTRALIAN: Secretary, 207, North Terrace, Adelaide.	All Contract Practice Appointments in South Australia. Booleroo Centre Medical Club.
WESTERN AUSTRALIAN: Honorary Secretary, 65, Saint George's Terrace, Perth.	All Contract Practice Appointments in Western Australia.
NEW ZEALAND (WELLINGTON DIVISION): Honorary Secretary, Wellington.	Friendly Society Lodges, Wellington, New Zealand.

Medical practitioners are requested not to apply for appointments to position at the Hobart General Hospital, Tasmania, without first having communicated with the Editor of THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

All communications should be addressed to "The Editor," THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, Sydney. (Telephones: MW 2651-2.)

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